The Effect of Exercise Training on Arterial Stiffness, Physical Function and Self-Reported Health in Haemodialysis Patients

By

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TABLE OF CONTENTS

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DECLARATION

This dissertation summarises original work conducted in the School of Human Life Sciences at University of Tasmania except where acknowledged otherwise.

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4th April 2010

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ABSTRACT

Haemodialysis patients show reduced physical function and greater risk of increased arterial stiffness because of hypertension, metabolic disturbances, and vascular calcification. Exercise interventions potentially could improve their vascular risk profile.

This randomized controlled study compared the effects of six months of supervised intradialytic exercise training versus home-based exercise training or usual care on arterial stiffness, physical function and self-reported health in 70 haemodialysis patients. Intradialytic-exercise patients trained three times/wk for six months on a cycle ergometer and home-based-exercise patients followed a walking program to achieve the same weekly physical activity. Usual-care patients received no specific intervention. Primary outcome measures were distance travelled during a six-minute walk test and aortic pulse wave velocity. Secondary outcome measures included augmentation index (augmentation pressure as a percentage of central pulse pressure), peripheral (brachial) and central blood pressures (measured noninvasively using radial tonometry), physical activity, and self-reported physical functioning.

Following six months of exercise intervention, there were no significant differences between changes in six-minute walk test distance (intradialytic exercise, +14%; home-based exercise, +11%; usual care, +5%), pulse wave velocity (intradialytic exercise, –4%; home-based exercise, –2%; usual care, –5%), or any secondary outcome measure.

In conclusion, there were no differences between intradialytic or home-based exercise training and usual care for vascular parameters, physical function or self-reported health in haemodialysis patients after the six-month intervention.

ABBREVIATIONS

AA	Active Australia Questionnaire
ADL	Activities of Daily Living
AIx	Augmentation Index (expressed as a percentage)
AIx@75bpm	Augmentation Index normalise to heart rate of 75bpm
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry
BDI	Beck's Depression Inventory
BMI	Body Mass Index
BP	Bodily Pain
bpm	Beats per minute (Heart rate)
CKD	Chronic Kidney Disease
$cm.s^{-1}$	Centimetres per second
cm^2	Centimetres squared- measurement of area
CVD	Cardiovascular Diseases
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GEE	General Estimating Equation
GH	General Health Score
HD	Haemodialysis
HR_{max}	Maximal heart rate
HB	Home-based Training Group
HRQoL	Health Related Quality of Life
ID	Intradialytic Training Group

IDT	Intradialytic Exercise Training
[K+]	Concentration of potassium ion
Kcal	Kilocalories
MAP	Mean Arterial Pressure
$Met.min^{-1}$	Metabolic equivalent
$Met.min^{-1}.week$	Metabolic equivalent per week
MH	Mental Health Score (SF-36)
$ml.min^{-1}$	Millilitres per minute
$ml.kg^{-1}.min^{-1}$	Millilitres per kilogram per minute (oxygen consumption)
mmHg	Millimetres of mercury pressure
$m.s^{-1}$	Metres per second (speed)
$m.s^{-2}$	Metres per second squared (velocity)
N	Newtons
Nm/kg*100	Newton per kg of bodyweight - measurement of torque
NDT	Non-dialysis day exercise training
Nm	Newton metres
PF	Physical Function Score (SF-36)
pH	Measurement of acidity
PP	Pulse pressure
PWA	Pulse wave analysis
PWV	Pulse wave velocity
RE	Role Emotional Score (SF-36)
RP	Role Physical Score (SF-36)
RPE	Rating of Perceived Exertion
SBP	Systolic Blood Pressure

SD	Standard Deviation
SF	Social Functioning Score (SF-36)
SF-36	Medical Outcomes Short-Form 36-Items Health Survey
SpKt/V	Single pool dialysis adequacy where K: dialyzer clearance of urea; t: dialysis time and V: patient's total body water
SVI	Stroke Volume Index
TUG	Timed-Up and Go Test
UC	Usual Care Group
VO_2max	Maximal Oxygen Consumption
VO_2peak	Peak Oxygen Consumption
VT	Vitality Score (SF-36)
W	Wattage
6MWT	Six-minute Walk Test

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 General Background

End-stage renal disease (ESRD) or renal failure describes a chronic and irreversible loss of kidney function. At this terminal stage of renal disease, patients in most cases, rely on renal replacement i.e. renal transplant or renal replacement therapies either by haemodialysis or peritoneal dialysis. In 2007, 16,770 individuals in Australia were treated for ESRD via renal replacement therapies (Australian Institute of Health and Welfare, 2009). The financial cost of kidney diseases to the health care system in Australia was $1.8 billion in 2005, with the annual cost predicted to reach $4.7 billion in 2010 with ESRD incurring the majority of these costs (Howard et al., 2006). In addition, other personal costs to patients and their care givers may include financial hardship, social disruption and psychological disorders (Australian Institute of Health and Welfare, 2009, Chow et al., 2003).

The kidneys perform multiple functions in maintaining homeostasis; therefore, the effects of ESRD may extend to physiological systems apart from the renal system. End-stage renal disease patients commonly present with co-morbidities that affect cardiovascular health, musculoskeletal structure, and metabolic function (Australian Institute of Health and Welfare, 2009). Examples of cardiovascular co morbidities may include left ventricular hypertrophy, hypertension and arterial diseases where atherosclerosis and arteriosclerosis are common (London, 2000). In addition, other metabolic complications such as hyperphosphataemia and hypercalcaemia in ESRD have been found to contribute to accelerated arterial calcification (Reynolds et al., 2004), leading to increased arterial stiffness in ESRD. Furthermore, the decreases in muscle mass as a result of uraemia (Johansen et al., 2003, Sakkas et al., 2003), along with an associated loss of muscle contractility (Fahal et al., 1997), result in physical function being markedly diminished. In addition to the changes in muscle function, another common feature in ESRD is poor bone density which is closely linked to low muscle strength (Spindler et al., 1997).

The pathophysiological effects of ESRD impact negatively on patients' health-related quality of life. Left ventricular hypertrophy and hypertension may decrease exercise tolerance which could potentially affect Activities of Daily Living (ADLs) such as grocery shopping. In addition, muscle atrophy as a consequence of uraemia, may limit physical function and hence decrease patients' physical activity levels. Indeed, ESRD patients have been observed to be some of the most sedentary individuals, even when compared to their healthy sedentary counterparts (Johansen et al., 2000). However, it has been found that regular exercise training over a period of a few months improves physical function and increases muscle strength (Storer et al., 2005) amongst other benefits, including improved health-related quality of life and psychosocial well-being (Kouidi et al., 1997). In view of the sedentary lifestyles that ESRD patients lead, these findings are significant to both ESRD patients and health care providers.

In addition to the economic costs and complications that arise with ESRD, the management of ESRD is labour intensive. In particular, patients on haemodialysis require the care of clinical nurses whilst admitted as in-patients receiving treatment at the renal units. This treatment can be as frequent as three to four times a week for three to five hours at a time, and patients may receive such treatment for years which can represent a huge economic cost. In addition, many patients may rely on care-givers and transport aides to ambulate to dialysis sessions (Australian Institute of Health and Welfare, 2009). Hence, from the health care provision perspective, the increase in physical function in ESRD patients obtained from regular exercise training may lead to increased independence resulting in greater ability of patients to self care and reducing the load on health care professionals.

1.2 Conceptual Background

The positive relationships between chronic kidney diseases and arterial stiffness mean that the length of time spent suffering from kidney diseases directly increases cardiovascular risk. This is evident in the high incidence of cardiovascular comorbidities and mortality in patients suffering from kidney diseases. The impact of kidney diseases extends to other physiological systems, as patients also suffer from other diseases that affect physical function. Hence, many patients' health-related quality of life is low, with a great proportion of patients suffering from depression and anxiety disorders. Previously, exercise studies in chronic kidney diseases and ESRD have reported positive results in improving patients' cardiovascular health, physical functioning and health-related quality of life. To date, only two studies have investigated the effects of exercise training on arterial stiffness in haemodialysis patients (Mustata et al., 2004, Toussaint et al., 2008b). While the supervised exercise training employed in these studies resulted in positive changes in arterial stiffness, this type of training requires additional manpower in the already labour-intensive service provision.

1.3 Significance of the Problem

According to the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA), cardiovascular disease has been the primary cause of mortality in this population (ANZDATA, 2008). Due to the multiple comorbidities in ESRD, patients are at greater risk of developing psychological problems such as anxiety and depression (Knight et al., 2003). End-stage renal disease patients remain one of the most sedentary clinical populations and the lack of physical activity can contribute to the already increased risk of developing cardiovascular diseases. Indeed, previous findings found that ESRD patients exhibit greater levels of arterial stiffness compared to similarly aged peers (Blacher et al., 1998a) which was correlated to a higher incidence of adverse cardiovascular events (Blacher et al., 1999). Hence, decreasing arterial stiffness would appear to be a good clinical marker to measure cardiovascular outcomes in ESRD populations. While pharmaceutical agents may have positive impacts on arterial stiffness, these are costly and may have other unwanted side effects. Hence, the investigation of an alternative therapy such as exercise training is warranted.

1.4 Purpose and Aims

The primary purpose of this thesis was to investigate the effect of two forms of exercise training, namely supervised intradialytic exercise training and home based walking, on arterial stiffness in ESRD. The effects of six months of unsupervised home based walking on physical fitness in ESRD was yet to be established; hence, a secondary focus of this study was to explore the effects of an unsupervised walking program on patients' physical function. While patients' physical function may be measured objectively with tests, self-reported physical function may provide some further insight into patients' subjective perception of their own health. Therefore, a third aim was to ascertain the effects of exercise training on patients' own subjective perceptions of their health and quality of life.

1.5 Research Questions

What are the effects of supervised intradialytic (training performed during haemodialysis session) and home-based exercise training on physical function, patients' self-reported health and arterial stiffness?

1.6 Hypotheses

The current research findings in the ESRD population suggest a possible relationship between physical function as measured by aerobic power and arterial stiffness. Firstly, this thesis hypothesizes that both intradialytic and unsupervised exercise training programmes would significantly increase physical function as well as decrease arterial stiffness. However, compared to unsupervised home-based walking, the intradialytic training programme is hypothesized to have a greater effect on physical function and arterial stiffness. Finally, this study hypothesizes that the changes in physical function following either exercise training programme would, in addition to the above changes, increase patients' self-reported health-related quality of life.

1.7 Significance of Study

The findings from this study add to the current body of literature outlining the effects of exercise training on physical function, cardiovascular health and self-reported health related quality of life in ESRD patients. Most importantly, in light of the high incidence of cardiovascular diseases in this population, it is hoped that the results would further the knowledge regarding the interaction between exercise, in particular an unsupervised home-based walking programme, and arterial stiffness in ESRD. Another important aspect of the study pertains to the feasibility and effectiveness of an unsupervised exercise training program outside dialysis compared to a supervised intradialytic cycling program over a period of six months. Walking is a very simple activity that may be performed regularly without the need of much equipment. It is thus hoped that the observations made from the unsupervised walking group would provide evidence to support the prescription of low to moderate physical activity such as walking to improve physical functioning in haemodialysis patients outside dialysis.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of Kidney Diseases

Kidney disease is characterised by the progressive loss of kidney function such that at end stage, which is also known as kidney failure, life may only be supported by renal replacement therapies including renal transplant, peritoneal dialysis and maintenance haemodialysis. The use of haemodialysis to manage the condition is labour and cost intensive, therefore it presents a huge burden to the community and economy. The estimated annual cost in Australian dollars to provide professional clinical and social support, as well as medication for a single inpatient haemodialysis patient was reported to be $82,764; satellite and home haemodialysis cost $48,631 and $44,739 respectively (Kidney Health Australia, 2009). Due to the close relationship between the regulatory functions of the kidney in expelling harmful waste products and the structural integrity of the cardiovascular system, risks of cardiovascular co-morbidities and mortality increase with advancing stages of renal disease. While dialysis of three to four times a week removes excess fluid and solutes, the build up of fluid and solute between treatments can still impact on cardiovascular structure and arterial health (Keven et al., 2008). This review will primarily focus on arterial remodelling and its effects in ESRD. Secondly, due to the multi-systemic co-morbidities that are common in kidney diseases, this review will discuss the effects of kidney disease on other physiological systems, which contribute to the impaired physical function. Lastly, the effects of cardiovascular comorbidities and lowered physical function on health-related quality of life in ESRD will be examined. The findings in this literature review will provide theoretical foundation for the methodology used in this thesis.

2.2 Fundamentals of the Arterial Pulse

The arterial system serves two purposes: *conduits* and *cushions* (London et al., 2002). As *conduits*, the arterial tree is composed of long branches of enclosed blood vessels supplying the various organs and tissues. Large arteries branching from the aorta extend and branch into smaller arteries, and finally into arterioles and capillaries at the tissue level. The oldest sign of life, the pulse that clinicians palpate occurs at such branching sites, is also the physical tell-tale sign of the *cushioning* function that arteries perform. There is variable pressure within the artery over every cardiac cycle. Hence, the principle guiding the measurement and application of arterial stiffness may be said to stem from the differences in pulse pressure waveforms that occur over the arterial tree (O'Rourke et al., 1992).

Present-day knowledge imparts that the characteristic stretching of the arterial wall caused by ventricular contraction may be palpated in "large, accessible" (O'Rourke et al., 1992) arteries such as the carotid, radial and femoral arteries by partially compressing the artery over the underlying bony surface i.e. applanation tonometry. Another common method of measuring arterial stiffness involves the use of Doppler ultrasound. Both techniques allow for the measurement of compliance of the arterial wall via pressure (mmHg) exerted on the arterial wall or pulsed wave Doppler velocity (cm/s^2) signal respectively and both methods of measurements have been reported to be highly valid and reliable instruments that have strong correlations with each other (Jiang et al., 2008).

2.2.1 The effects of Age on Arterial Stiffness

Arterial stiffness is a natural phenomenon that increases with age in healthy populations. This is due to arterial remodelling which is characterised by structural changes to the intima media of the vascular wall. An example of this change is in the breakdown of the orderly network of elastic lamellae of the intima media which is replaced by a haphazard arrangement of fibres as part of the ageing process. This can result in decreases of the overall ability of the intima media to withstand pulsatile pressures. The intima media may also thicken in the process. Such intrinsic change within the arterial wall is known as *arteriosclerosis* where arteries become stiff, tortuous and dilated. *Atherosclerosis*, a second form of arterial remodelling, involves the formation of plaques that reduce the luminal surface of the arteries. Both arteriosclerosis and atherosclerosis are forms of arterial remodelling that may impact on the cushioning function of arteries by impeding blood flow and distensibility (London et al. 2002).

2.2.2 The Link between the Heart, Blood Vessels and the Kidneys

Chronic renal disease populations are predisposed to stiff arteries due to metabolic and biochemical imbalances that occur due to impaired renal function (Blacher et al., 1998a). Research has shown that the arteries of chronic renal disease patients are stiffer than in healthy individuals and that cardiovascular structure and function in ESRD is vastly different to that of healthy populations (London et al., 1996). This suggests that renal diseases contribute to the acceleration of arterial stiffness.

The homeostatic balance of the body’s internal environment is achieved primarily by the ability of the kidney to filter excess fluid, harmful metabolic wastes and other solutes. In kidney diseases, the inability to maintain homeostasis of pH, electrolyte and mineral concentration, and plasma volume result in the accumulation of fluid and metabolic waste products. The most direct effect on the cardiovascular system is increased plasma volume exerting a greater pressure within the arterial tree. Chronic hypertension may cause hypertrophy of the myocardium in the left ventricle as an adaptation to the increased pressures associated with chronic fluid overload. In addition, the structure of the arterial wall may undergo arterial remodelling i.e. dilatation and/or thickening in response to increased volume and pressure. Such physiological adaptations may result in a range of cardiovascular pathological conditions common in ESRD (London et al., 2002).

2.2.3 Mechanisms of Arterial Modifications in ESRD

There is a positive relationship between the progress of chronic kidney diseases and arterial stiffness (Keven et al., 2008, Wang et al., 2005). Wang et al. (2005) found greater incidences of arterial stiffness in patients at later stages of chronic kidney diseases; the increase in arterial stiffness was reported to continue despite maintenance haemodialysis. In an interesting study comparing haemodialysis and renal transplantation patients with healthy controls, Keven et al. (2008) reported that haemodialysis patients had significantly stiffer arteries (p=0.040) compared to normal control. Pre-transplantation, patients also exhibited significantly stiffer arteries (p=0.038) compared to normal controls but there was a significant difference in the change in pulse wave velocity between the haemodialysis group and the renal transplantation group (p=0.01), which suggests that the long term effect of renal transplantation greatly reduces arterial stiffness in ESRD patients. Keven et al. (2008) also reported a significant corresponding decrease in serum phosphate 12-month following transplantation, which may contribute to a potential reduction in arterial calcification in ESRD (London et al., 2002) providing a potential mechanism for the improvements observed in arterial stiffness post transplantation.

In ESRD, age-related arterial remodelling is exacerbated by several associated comorbidities. Besides hypertension, other factors play important roles in affecting the compliance of the arterial wall. Biochemical disturbances such as uraemia, hyperphosphotaemia and hypercalcaemia may contribute to the haphazard arrangement of the collagen fibres within the arterial wall, giving rise to decreased distension (Blacher et al., 1998a). Potential mechanisms behind arteriosclerosis and hence increased arterial stiffness in ESRD increase in the haphazard formation of collagen fibres within the endothelium (London et al., 2002), resulting in a loss of compliance or ability of the endothelial wall to absorb pulsatile pressures. The ‘hardening’ of the arterial wall in arteriosclerosis may be further exacerbated by increased levels of free extraosseous calcium within plasma and interstitial fluid that binds to soft tissues such as the endothelium (London et al., 2004), In addition, extraosseous calcium may also contribute to atherosclerosis when calcium binds to plaques on luminal walls, forming calcified plaques. The consequences of arteriosclerosis and atherosclerosis in ESRD are reduced vascular compliance and increased blood flow velocity, which result in hypertension and left ventricular hypertrophy (Agarwal et al., 2003) and consequently cardiovascular and coronary heart diseases (London et al., 1999).

2.2.4 Increased Blood Volume and Hypertension in ESRD

The vascular network is comprised of a series of arteries, capillaries and veins within an enclosed network. In normal populations, systolic blood pressure of more than 140 mmHg and diastolic blood pressures of more than 90mmHg are clinical markers of hypertension. This classification of hypertension is applied across all populations including renal populations where normal blood pressures range around 120/80 mmHg and values above 130/85 are considered to be pre-hypertensive. Blood pressure may increase for several reasons including arteriosclerosis and atherosclerosis. In ESRD, the accumulation of excess fluid increases the total volume of fluid within the vascular network, thereby increasing the pressure within the vasculature (secondary hypertension). Such an increase in blood pressure is common in ESRD. Thus while increased blood pressure in ESRD is a direct consequence of a host of pathological reasons, increased blood volume is generally considered to be a major contributor. Studies investigating the effects of antihypertensive medication in ESRD have reported positive changes in blood pressure and as a consequence are of significant clinical value in the management of secondary hypertension (Ichihara et al., 2002, Baber et al., 2007).

2.2.5 Extraosseous Calcium and Hyperparathyroidism in ESRD

Imbalances of mineral metabolism in progressive chronic kidney disease can result in high levels of extraosseous calcium circulating in the bloodstream which may contribute to arterial stiffening. The effects of calcium, in particular extraosseous calcium on arterial stiffness have been reported previously (London et al., 2004). The common roles that calcium plays in human physiology include bone synthesis and muscular contraction. In healthy states, the bones function as storage space for calcium. However, in kidney diseases, imbalances in phosphate metabolism can increase the circulating levels of plasma calcium, a homeostatic imbalance that has been reported to increase the incidence of cardiovascular disease in ESRD (Goodman et al., 2000, London, 2003). The high-affinity between phosphate and calcium causes calcium to be leached from bones into the systemic circulation, which in turn contributes to the calcification of soft tissues such as arteries. In a study comparing the degree of vascular calcification between young ESRD patients and age-matched healthy controls, using electron-beam computed tomography, Goodman et al. (2000) found that 14 of 16 ESRD patients between 20 and 30 years of age presented with evidence of coronary artery calcification. This compared to only 5% of 60 similarly aged healthy controls who demonstrated the same degree of calcification. London et al. (1999) described such high degrees of calcification to be of great clinical significance to cardiovascular mortality in ESRD as patients that exhibited high degrees of arterial calcification were found to have significantly stiffer arteries than patients that exhibited lower degrees of calcification (London et al., 1999). Previously increased arterial stiffness indicated by a high pulse wave velocity has been reported to increase cardiovascular and overall mortality with a 1 $m.s^{-1}$ increase in aortic pulse wave velocity reported to increase mortality risks by 14% in 242 ESRD patients (Blacher et al., 2003). These studies show that uremic calcification increases the risk of cardiovascular diseases and mortality. In ESRD, metabolic factors such as calcium and phosphate levels, pharmaceuticals and renal replacement therapy have all been found to affect arterial stiffness (Toussaint et al., 2008a, Tziomalos et al., 2007, Keven et al., 2008). In a cross-sectional study of 48 chronic kidney disease (eGFR = 35.1 ± 10.5 $ml.min^{-1}$) patients aged between 26 and 80 years, Toussaint et al. (2008a) found positive relationships between pulse wave velocity and a range of biochemical markers related to calcium and hyperparathyroidism..

Toussaint et al. (2008a) reported positive relationships between vascular calcification and PWV (r=0.42; p=0.008) in mild kidney disease patients (eGFR: 17-55 $ml.min^{-1}$), which highlights the early onset of vascular calcification with small reductions in renal function. Vascular calcification is partly related to plasma phosphate levels, which have been found to be higher in haemodialysis patients (London et al., 2004). It has also been reported that a high serum phosphate level was significantly related (p=0.37) to the degree of vascular calcification. This relationship between serum phosphate and vascular calcification was further examined by Toussaint et al. (2008a) who found positive correlations between phosphate and calcium-phosphate product and PWV (r=0.35; p=0.02). Control of circulating concentrations of these minerals via diet and/or phosphate binders therefore are important considerations for ESRD patients (Tziomalos et al., 2007).

Hormonal regulation of the levels of calcium and calcium-phosphate compounds in ESRD can often be affected by secondary hyperparathyroidism. London et al. (2004) determined that high serum parathyroid hormone is highly associated with arterial stiffness in ESRD patients ($p < 0.01$). Parathyroid hormone, released by the parathyroid gland when blood levels of ionic calcium are low, provides hormonal control of serum calcium concentration by indirect stimulus on osteoclasts, thereby destroying bone and freeing-up calcium. This extraosseous calcium may bind to triglycerides and low-density lipoprotein cholesterol in blood which in turn may be deposited on the walls of arteries, giving rise to atherosclerosis. This indicates that vascular calcification may be exacerbated by high levels of triglycerides, and lipid-lowering agents have proven to be effective in lowering arterial stiffness. (Efrati et al., 2007, Dogra et al., 2007) When examining the degree of arterial calcification in the common carotid, abdominal and femoral arteries, London et al. (2004) found that patients who took higher dosages of calcium-carbonate, a widely prescribed phosphate-binding agent, had increased vascular calcification. A host of antihypertensives that act on blood viscosity, endothelial wall and cardiac rhythm and output are available in the treatment of cardiovascular diseases. Some of these medications have been found to be effective in regulating blood pressure i.e. lowering systolic blood pressure and pulse pressure, therefore managing cardiovascular conditions. (Van Bortel et al., 1999) However, these medications also have various side effects such as lethargy, dizziness, shortness of breath, blurred vision and heartburn (MIMS Australia, 2009) which therefore may affect patients' quality of life.

2.3 Pulse Wave Measures of Vascular Function

The measurement of arterial stiffness may provide greater insight to the management of cardiovascular risks in ESRD. As previously discussed in section 2.2 (p.7), there are many factors contributing to the increases in arterial pressure. In addition, there are strong correlations between pulse wave velocity and risk of cardiovascular mortality in ESRD populations. Conventional detection of hypertension requires the measurement of systolic and diastolic blood pressures which are usually derived from brachial blood pressure cuff sphygmomanometry. This method determines how much pressure is generated during ventricular contraction (systole) or ventricular relaxation (diastole). Accepted norms for systolic and diastolic blood pressures at rest are <120 mmHg and <80 mmHg respectively. Calculations of other important derivatives such as pulse pressure (PP) or mean arterial pressure (MAP) may also be performed. Pulse pressure informs of cardiac output where low pressure values indicate low stroke volumes common in congestive heart failure while mean arterial pressure indicates perfusion pressure needed for the adequate perfusion of organs with nutrient-rich blood. However, while the measurement of blood pressure provides information pertaining to the health status of the cardiovascular system, it does not adequately measure the cushioning function of arteries; nor does it take into account the idiosyncrasies of the interaction between the heart, arteries and the body of fluid that is being transported within the arterial tree. Measurement of arterial stiffness should therefore be added to the conventional measure of blood pressure when examining the health of the vascular structure (Izzo, 2005).

The distensibility of the conduit vessels allow for the cushioning of pressure exerted by each ventricular contraction. This quality of arteries may be characterised by the degree of augmentation of reflected pressure waves and by the velocity of each pulse wave (O'Rourke et al., 1992). Recent advances in technology have seen the measurement of pulse waves evolve from invasive methods using an electromagnetic flow meter which can either be applied around an artery or incorporated into a catheter inserted into an artery, to simple non-invasive methods such as Doppler-ultrasound and applanation tonometry that produce excellent results (Liang et al., 1998, Savage et al., 2002, Wilkinson et al., 1998). Doppler-ultrasonic probes (Tanaka et al., 2000, Savage et al., 1998) and high-fidelity applanation tonometers (London et al., 1996, Tanaka et al., 2000, Toussaint et al., 2008b) can be applied over the skin of an accessible artery to measure arterial stiffness. Applanation tonometry is the chosen method of this thesis and hence will be described principally.

The principle of applanation tonometry is based on the interaction between the distensibility of arterial walls and the pressure waves that are generated with each ventricular contraction. The physical laws that govern this interaction include fluid viscosity, shear stress and circumferential stress. Put simply, the cushioning function of the arteries may be examined by measuring the amount of force i.e. pressure (mmHg), which is exerted against the tonometer compressing an artery over an underlying bone throughout the pressure wave. This technique has proven to be valid, as shown by its ability to independently predict cardiovascular events in several studies (Blacher et al., 1998b, Zoungas et al., 2007) and it has produced reliable results (Wilkinson et al., 1998, Zoungas et al., 2007). Wilkinson and colleagues (2000) reported a significant inverse linear relationship between augmentation (increase in pressure of the reflected wave back to the aorta) and heart rate ($r=0.76$; $p<0.001$). In comparing the differences between Doppler-ultrasound and applanation tonometry when measuring arterial stiffness, Liang et al. (1998) compared the relationships of the two measurement technique with vascular parameters and reported high repeatability as well as interrelationship between pulse wave velocity and vascular structure. Another study that investigated the relationship between indices of arterial stiffness and cardiovascular events in kidney diseases found significant hazard ratios for every 1 $m.s^{-1}$ increase in pulse wave velocity (PWV) (hazard ratio- 1.14; $p<0.001$) and PWV exceeding 9.9 $m.s^{-1}$ compared to PWV less than 9.9 $m.s^{-1}$ (hazard ratio- 3.38; $p<0.001$). (Zoungas et al., 2007) In a study investigating biochemical alterations in ESRD (Blacher et al., 1998a), arterial stiffness measured via applanation tonometry showed significant positive relationships between pulse wave velocity and markers of cardiovascular risks such as systolic blood pressure, ($p<0.01$) aortic calcification ($p<0.01$) and diabetes mellitus ($p<0.0043$).

Using the SphygmoCor™ System (AtCor, Sydney, Australia) of applanation tonometry, two measurements: Pulse Wave Analysis (PWA) and PWV may be performed. Both measures rely on blood flow and pressure wave transmission and reflection. Pulse wave analysis measures pulse pressure wave reflection from only a single peripheral pulse i.e. radial artery at the wrist and therefore is the degree of augmentation of the reflected pressure waves back to the aorta i.e. incident and reflected wave pressures. These data hold clinical significance as the degree of arterial stiffness may be quantified in mmHg. The data collected from augmentation may be used to calculate a percentile value to derive an *augmentation index* (AIx). The reference ranges for augmentation index for normal, healthy populations lie between 4.7% to 41.5% for ages 20 to 80 years. This compares to AIx values found in competitively and recreationally trained individuals where values may lie between -2.1% ± 2.1% and 4.5% ± 2.9% respectively (Edwards and Lang, 2005). This value may also be normalised to account for heart rate by normalising the value to heart rate of seventy-five beats per minutes (AIx@75bpm). While AIx provides absolute value to the degree of augmentation, AIx@75bpm allow for the comparison/examination of augmentation in relation to heart rate. Hence, AIx@75bpm may provide further insight into the degree of amplification of the reflected pressure wave to the heart.

Pulse wave velocity, on the other hand, measures the speed at which the pressure waves travel along a region of a known artery i.e. between two pulse sites such as the carotid and femoral pulses. Carotid-femoral PWV has been suggested to be the current gold standard in the measurement of arterial stiffness due its predictive value for cardiovascular events (Blacher et al., 1998b, Laurent et al., 2006). In addition, pulse wave velocity requires minimal technical expertise (Laurent et al., 2006) and hence, may have a lower inter-tester variability than pulse wave analysis. Using applanation tonometry, the time taken for a pulse wave to travel from one point to the next, over a known distance is used to calculate pulse pressure wave velocity in $m.s^{-1}$. Aortic pulse wave velocity may be measured between the carotid and femoral pulse while peripheral pulse wave velocity may be measured using the carotid and radial pulses. Hence, the presence of accelerated arterial stiffness in ESRD patients may be determined.

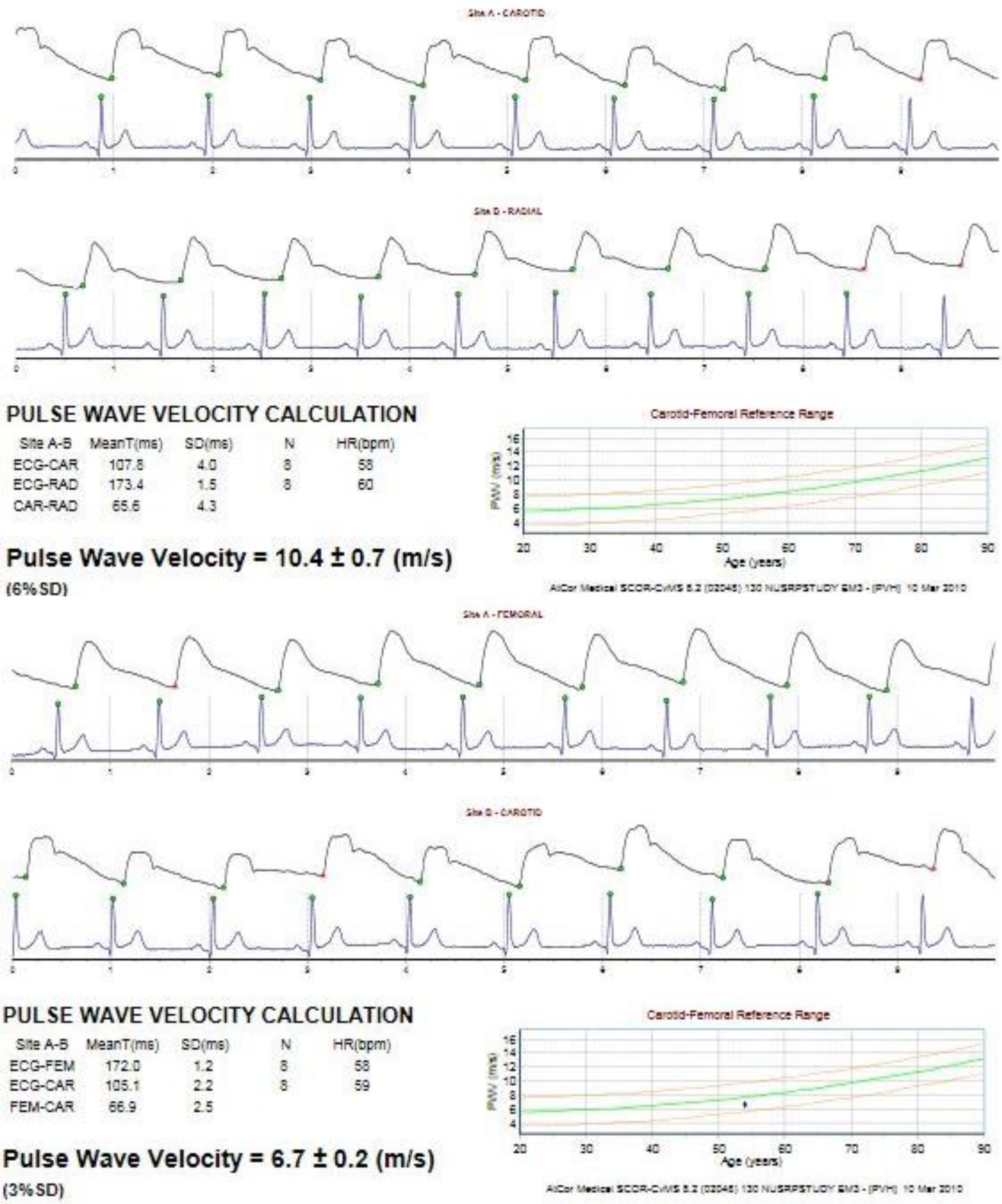

Figure 2.1. Typical pulse pressure waveforms taken during the measurement of pulse wave velocity. Carotid, radial and femoral arteries are shown: In general, pulse pressure waves measured from the carotid, radial and femoral arteries have distinct shapes that are peculiar to the individual sites. The various arteries thus have different cushioning attributes with proximal arteries typically more elastic than distal arteries (Laurent et al., 2006).

2.3.1 Factors Affecting Arterial Compliance in Healthy Individuals

Arteries serve as conduits and cushions in the transport of blood around the body. The cushioning function, which is determined by arterial compliance, is made possible because of the physiological structure of the tunica media and adventitia which can change over time. The arteries are highly elastic tissues which are comprised of simple squamous endothelial cells connected by a dense network of connective tissues composed of collagen and elastin fibres (Marieb, 2001). The compliance and hence the cushioning function of the arteries depends on the integrity as well as the structural arrangement of these connective tissues. Three major factors that affect arterial compliance, and hence contribute to arterial stiffening are age, gender and level of physical activity (Tanaka et al., 2000, Vaitkevicius et al., 1993). The mechanisms by which age, gender and level of physical activity affect arterial compliance in apparently healthy individuals are discussed in greater detail below.

2.3.2 Age and Arterial Health

In healthy normotensive individuals, age consistently plays a significant role in arterial compliance (Vaitkevicius et al., 1993, McVeigh et al., 1999). An early study (Kelly et al., 1989) investigated the effect of age on carotid, radial and femoral pulse pressure waves in 1005 healthy subjects using applanation tonometry. Using a cross sectional design, the amplitude of the pulse pressure in the carotid, radial and femoral arteries were compared in subjects across a range of ages from the first to the eighth decade of life and was found to increase by 91.3%, 67.5% and 50.1% respectively. The 91.3% increment in amplitude of the pulse pressure in the carotid artery was the consequence of an increase in augmentation index from 1.6% in the first decade of life to 24.1% in the eighth decade. Similar patterns reported by Vaitkevicius et al. (1993) also found major age-associated differences in arterial compliance in a group of 146 healthy, normotensive volunteers aged between 21 and 96 years. Their results indicated that pulse pressures (systolic blood pressure minus diastolic blood pressure) were greater in older men (36.8%; $p<0.001$) and women (47.3%; $p<0.005$) compared to younger individuals; resulting in increases in augmentation index and aortic pulse wave velocity by five and two folds respectively. In another study, McVeigh and colleagues (McVeigh et al., 1999) reported the effect of ageing on arterial compliance using applanation tonometry of the radial pulse in 212 healthy individuals aged between 21 and 83 years (147 women and 65 men). Large artery compliance was found to be 35% lower ($p<0.001$) and systemic vascular resistance was higher by 66% ($p<0.001$) in the third compared to the ninth decade of life. Only a single study has investigated the effect of ageing on pulse wave velocity (Avolio et al., 1983). Pulse wave velocity in 480 subjects aged between 3 and 89 year were examined and it was reported that pulse wave velocity increased significantly with age by 134% ($p<0.001$) across the age group studied. Thus there is overwhelming evidence regarding the effects of age on arterial stiffness.

2.3.3 Physical Activity and Arterial Health

Lifestyles have significant bearings on human arterial compliance. Participation in regular physical activity provides a potential defence against cardiovascular diseases as well as a tool for the improvement of physical function (Tanaka et al., 2000, Vaitkevicius et al., 1993). Kingwell and colleagues (Kingwell et al., 1997) also found significant acute effects such as decreased aortic and femoral pulse wave velocities ($4 \pm 2\%$, $p<0.04$; $10 \pm 4\%$, $p<0.01$) following a single 30-minute cycling session at an intensity equating to 65% of VO_2max. However, the acute effects on arterial stiffness had disappeared by one hour post exercise. In another study, Tanaka and co-workers (Tanaka et al., 2000) examined arterial stiffness in 151 men aged between 18 and 77 years of age, who were grouped according to their physical activity levels. This study had two stages where the first stage followed a cross-sectional study design and the second stage followed a single group interventional study design. The cross sectional study indicated that there is a significant effect of chronic exercise on arterial compliance where endurance trained men exhibited 35% higher arterial compliance ($p<0.01$) than their sedentary and recreationally active counterparts. In the interventional stage of the study, the authors (Tanaka et al., 2000) examined the effects of a walking intervention on arterial compliance in twenty men from the sedentary group of fifty-four men, aged 54 ± 2 years. Three months of regular walking at intensities between 60% and 75% of maximal heart rates for 30 to 45 minutes three to six times per week, resulted in a 25% increase ($p<0.01$) in arterial compliance. These post-intervention values of arterial compliance were comparable to those observed in the endurance trained groups of similar ages (Tanaka et al., 2000). These findings (Tanaka et al., 2000) were supported by another study that compared healthy individuals and similarly aged athletes' aerobic capacity and arterial stiffness (N=146; 21 to 96 years old) (Vaitkevicius et al., 1993). Cardiorespiratory fitness measured by the maximal oxygen consumption (VO_2max; $ml.kg.min^{-1}$) was reported to be inversely correlated to PWV ($p<0.01$) and AIx ($p<0.0001$), which supported Tanaka et al.'s (Tanaka et al., 2000) findings of increased arterial compliance following aerobic type training. Thus the current evidence supports the hypothesis that arterial stiffness can be lowered through participation in regular aerobic exercise training.

The focus of this section of the review so far has been on the effects of aerobic exercise training on arterial stiffness. However a number of studies have examined the effects of other forms of exercise such as resistance training and a number of papers suggest that resistance training, in particular concentric versus eccentric type training, elicits negative modifications of vasculature and left ventricular hypertrophy (Miyachi et al., 2003, Bertovic et al., 1999, Okamoto et al., 2006). However, one study has found no negative effects (Yoshizawa et al., 2009); hence while not all studies (Yoshizawa et al., 2009, Heffernan et al., 2009) reported positive effects of resistance training on arterial stiffness, it may be due to the sample size and techniques of resistance training. Resistance training may have positive effects on microvascular function but not central artery stiffness (Heffernan et al., 2009). These results in healthy populations suggest that although resistance training has many positive effects such as increasing functional strength, it may not be an appropriate form of exercise intervention in haemodialysis patients to lower arterial stiffness with the possible exception of eccentric resistance training.

2.4 Physical Function and Disability in ESRD

2.4.1 Physical limitations in Chronic Kidney Diseases

Physical functioning may be described as a person’s ability to perform day-to-day tasks and may encompass components of physical fitness such as cardiopulmonary fitness, muscle strength, and general locomotor skills (Painter et al., 1999). Renal disease patients have been found to exhibit lower physical functioning compared to age and sex-matched healthy controls (Blake and O'Meara, 2004). In kidney diseases, conditions such as uraemia, metabolic acidosis, and pH and mineral imbalances may affect physical capacity and exercise tolerance. The effects of calcium and phosphate metabolism on bone health (Salusky and Goodman, 2001) and the effects of uraemia on muscle structure (Johansen et al., 2003, Fahal et al., 1997) and therefore the physical limitations in ESRD populations have been well documented. Within the ESRD population, osteoporosis and fractures due to falls are common. In fact, the incidence of fractures is associated with muscle strength in ESRD (Jamal et al., 2006). In addition, it has been reported that a sedentary lifestyle was a major contributor to low physical function (Painter et al., 2000). On the other hand, the low physical function observed in ESRD limits patients’ motivation to become physically active (Goodman and Ballou, 2004). Hence, there is an interesting relationship between physical functioning and physical activity levels. Some patients have reportedly attributed the risk of falls as one of the main reasons for not participating in any physical activity while other patients report low physical strength as their main reason for low physical activity levels (Blake and O'Meara, 2004). Additional reasons for low physical activity were associated with nutritional status and complications that arise from maintenance dialysis (Johansen et al., 2000). Nevertheless regular physical activity has been found to increase physical functioning in renal diseases (Johansen, 2005). Hence, while low physical functioning may be due to several physiological reasons that are not within the control of ESRD patients, physical activity may alleviate the detrimental effects of kidney diseases on physical function and the quality of life. Whether low physical function affects physical activity levels or vice versa, the potential consequence is disablement (Tawney et al., 2003, Johansen et al., 2000) and reduced survival in the haemodialysis population.

While some factors contributing to the sedentary lifestyles may be uncontrollable, physical function may still be measured as a way of monitoring patients' degrees of disability and their quality of life. The evaluation of physical function has largely been determined by patients' ability to perform activities of daily living (ADLs). These ADLs may include tasks such as bathing, grooming, toileting, transferring, and ambulation (Lawton and Brody, 1969), and considered to be necessary for basic personal care and independent living and hence quality of life in ESRD. As a result of deterioration in physiological function such as lowered VO_2peak and muscle strength in ESRD patients, the ability to perform ADLs such as grocery shopping and regular ambulation may be impaired. The ability to perform ADLs may include functional fitness tests such as the six-minute walk test, timed up and go test, stair-climbing and sit-to-stand tests that establish physical capacities such as muscular endurance and agility which are both important in carrying out daily tasks. These tests have been designed for and used in a range of populations (Podsiadlo and Richardson, 1991, Storer et al., 2005). An example of a test that measures functional fitness is the six-minute walk test which provides a measure of exercise capacity and has been used widely with geriatric, diabetic, cardiovascular disease, pulmonary disease, and kidney disease patients (Green et al., 2001, Parsons et al., 2006). Eight weeks of intradialytic training in ESRD patients have been reported to significantly increase the distance walked in six minutes

($p<0.05$) compared to controls (Painter et al., 2000). In addition to the improvements reported in the measures of physical function, similar changes were also found in the self-reported health in the intervention group through the use of the 36-items Medical Outcomes Short Form Health Questionnaire (SF-36). This finding suggested a close relationship between patients' physical functioning and self reported health. In Blake and O'Meara's (Blake and O'Meara, 2004) study, the authors also reported that even high-functioning ESRD patients who scored between 75 – 95 (out of a possible 100) on the SF-36 physical function score were significantly limited in their physical functioning, measured using isokinetic and isometric leg muscle strength testing. Amongst the tests performed, isometric (static) peak torque was 134 ± 63Nm in renal patients compared to 203 ± 60Nm in healthy controls ($p<0.05$), and maximal walking speed in renal patients was 1.74 ± 0.18 ms^{-1} compared to 1.59 ± 0.21 ms^{-1} in healthy controls ($p<0.01$) (Blake and O'Meara, 2004). Another common and reliable measure of aerobic capacity and muscular endurance in ESRD patients is the six-minute walk test. The six-minute walk tests in 60-69 year olds were previously reported to be 572 ± 92m and 538 ± 92m for healthy males and females respectively (Steffen et al., 2002). This compares to findings within the ESRD population of 522 ± 46 m at the ages of 42.8 ± 4.4 years (Headley et al., 2002). These results suggest that middle-aged renal patients' muscular endurance and cardiorespiratory fitness as measured by the six-minute walk test are lower than those of older healthy individuals. Results from some studies in ESRD populations show that patients consistently exhibit low physical capacities when compared to findings of other studies that examined other populations of similar ages (Table 1).

Table 2.1. Comparison of Physical Function in ESRD and Normal Populations.

Author (Date)	N ESRD/Controls	Age	Physical functioning parameters	ESRD	Controls	Significance
Blake and O'Meara (2004)	12/12	18-55	SF-36 [median (range)] Isometric (static) peak torque (Nm/kg*100) Maximal Walking Speed (ms^{-1}) Sit-to-stand test (s)	85 (75 – 95) 134.3 (62.8) 1.74 (0.18) 10.1 (1.6)	100 (90 – 100) 203.0 (59.8) 2.05 (0.29) 7.3 (1.1)	0.001 0.05 0.01 0.001
Johansen et al. (2001)	46/0	52 ± 17	Gait speed (ms^{-1}) Stair Climbing Test (s) Chair Rising time (s)	113.1 ± 34.5 10.3 ±7.7 16.6_9.5	- - -	
Johansen et al. (2003)	38/19	55 ± 15/ 55 ± 13	Maximal Voluntary Contraction (N) Contractile Cross-sectional area (cm^2) Noncontractile Cross-sectional area (cm^2)	169.6 ± 65.5 7.2 ± 3.1 3.7 ± 2.3	217.7 ± 69.1 9.1 ± 2.0 1.8 ± 0.5	0.03 0.02 0.001
Sangkabutra et al.(2003)	9/8	26 ± 4 / 24 ± 6	Peak Oxygen Consumption ($ml.kg.min^{-1}$)	24.5 ± 2.3	43.7 ± 1.5	0.001

Data from studies presented in this table is shown as mean ± SD.

2.4.2 Factors Affecting Exercise Tolerance in ESRD Populations

The effects of kidney disease on exercise tolerance and physical capacity have been well examined (Painter et al., 2000, Johansen, 2005). Various potential factors associated with renal diseases may affect physical function and thus physical capacity. Such factors may include uremic myopathy (Johansen et al., 2003), anaemia (Breiterman-White, 2005, Robertson et al., 1990), and metabolic dysfunction (Armstrong et al., 2006). An important finding associated the loss of active muscle tissues to pH levels in ESRD patients (Johansen et al., 2003). In ESRD, muscle tissues are subjected to atrophy when physiological environments such as pH levels change during metabolic acidosis (Johansen et al., 2003). The loss of muscle mass and/or contractile muscle tissue may contribute to the lowering of physical capacity, which is further exacerbated by low levels of physical activity (Johansen et al., 2000). Johansen et al. (Johansen et al., 2003) found significantly lowered maximal voluntary contraction force in haemodialysis patients (169.6 ± 65.5 N) compared to healthy controls (217.7 ± 69.1 N) ($p=0.03$). The decreased strength in haemodialysis patients was correlated to the significantly smaller cross-sectional areas of contractile muscle tissue ($p=0.02$) compared to healthy controls. In addition, the haemodialysis patients studied also exhibited greater areas of non contractile muscle tissue compared to healthy controls ($p=0.001$). While muscle strength is affected by muscle contractility, haemoglobin levels contributed to aerobic power in haemodialysis patients. Robertson et al. (1990) reported significant improvement in aerobic capacity following recombinant erythropoietin therapy in 19 anaemic haemodialysis patients (baseline VO_2max: 15.3 ± 5.4 $ml.kg.min^{-1}$ and baseline maximal heart rate:139 ± 24 bpm). However, the VO_2max results at the end of the study were still below those of older healthy sedentary individuals whose VO_2max ranged from 22.2 ± 3.1 to 27.2 ± 5.1 $ml.kg.min^{-1}$ (Ogawa et al., 1992). In another study of 9 haemodialysis patients, VO_2peak was reported to be significantly ($p<0.001$) lower than in healthy controls. Sangkabutra et al. (Sangkabutra et al., 2003) found significant correlations between the graded exercise test to assess VO_2peak and plasma $[K^+]$ which suggested that impaired potassium regulation in kidney diseases contributes to early muscle fatigue, resulting in reduced exercise performance.

The decrements in physical function in ESRD may also impact on patients' self-esteem, therefore resulting in patients' negative assessments of their own physical function. End-stage renal disease patients' subjective reports of physical functioning have been found to be lower than actual or objectively measured physical functioning (Blake and O'Meara, 2004). This may be one major reason for ESRD patients' largely sedentary lifestyles. Compared to normal sedentary populations, ESRD patients are even more inactive. In a vicious cycle, ESRD patients' fitness levels fall even lower the longer they stay sedentary and because their fitness levels are low, their tolerance for physical activity is lowered, thereby creating a greater inertia when trying to increase physical activity (Painter et al., 2000, Johansen et al., 2000).

2.6 Health-Related Quality of Life in ESRD

The combined effects of chronic kidney diseases on the physical as well as psychological functions on patients may contribute to a diminished quality of life. Health related quality of life (HRQoL) is often measured in ESRD patients using questionnaires or functional tests and may be defined as patients' perceived quality of life such as physical and social function with regard to their health status (Ware et al., 1997). HRQoL has been observed to be lower than normal healthy populations (Ouzouni et al., 2009, Padilla et al., 2008, Painter et al., 2000). In many studies of ESRD patients, quality of life reflects the extent of disease (Kalantar-Zadeh et al., 2001, Knight et al., 2003, Kouidi, 2004) with the lowest HRQoL in those with the worst prognosis. Various questionnaires and inventories have been used to measure ESRD patients' perceptions of their physical, mental, emotional and psychological functions. These assessment tools have consistently found low functioning status in all of the above parameters compared to general populations' norms. In a large study of 14,815 haemodialysis patients, Knight et al. (2003) found a close relationship between self-reported mental and physical function and 1-year mortality using the SF-36 Questionnaire. Another study (Zimmermann et al., 2006) which used the Beck Depression Inventory (BDI) found that depression was a strong predictor of quality of life. Measurements of the 21-item BDI (score range: 0 'minimal intensity of depression' – 63 'severe depression') included psychological parameters such as sadness, hopelessness, lack of pleasure and guilt, and somatic symptoms such as sleep and appetite disturbances. Significant depressive symptoms were inversely correlated with some SF-36 items such as physical function ($p=0.004$), role-physical ($p=0.022$), bodily pain ($p=0.038$), general health ($p=0.015$) and vitality ($p=0.031$). where the presence of mild depression with BDI scores of ≥10 greatly impacts on quality of life (Zimmermann et al., 2006). In another study (Kalantar-Zadeh et al., 2001a), SF-36 scores were found to have significant clinical correlations with serum albumin ($p<0.01$) and haemoglobin levels ($p<0.01$). This study also found an inverse relationship between SF-36 scores and BMI, indicating that overweight and obese patients had lower HRQoL (Kalantar-Zadeh et al., 2001a). Low self-efficacy and self-esteem may translate into higher dependency on care-givers and depression (Painter et al., 2000).

2.6 Exercise Studies in ESRD

As discussed earlier (p.6), ESRD may be managed by haemodialysis, peritoneal dialysis or renal transplant, and exercise training in these different situations requires special considerations. Due to the link between physical function and survival in ESRD (Sietsema et al., 2004) and the understanding that regular exercise training improves physical function in healthy and diseased populations, exercise may be considered to be a potential treatment modality in ESRD. (Table 2.2)

Table 2.2. Exercise Studies in Haemodialysis Patients.

Author (year)	n	Study groups	Exercise intervention				Outcomes		p
			delivery	modality	prescription	duration	Variable	% change	
Kouidi et al. (1998)	7	HD	Combination of aerobic and resistance	NDT; aerobic, callisthenics; swimming, ball games, low resistance	90 mins x 3/week	6 mths	VO_2peak Blood lactate at VO_{2peak} Maximal Isometric Force Muscle morphometry	↑ 48% ↓ 16% ↑ 40-56% ↑↑↑↑↑	<0.05 <0.05 <0.05 <0.05
Mustata et al. (2004)	11	HD	Aerobic (conditioning exercises)	NDT; callisthenics, resistance and aerobic exercises	1hr x 2/week 134% of pre-exercise resting HR on recumbent bicycles or treadmill	3 mths	Arterial Stiffness Pulse Pressure	↓ 28% ↓ 11%	≤0.01 <0.05
Parsons et al. (2006)	13	HD	Aerobic	IDT; cycling and stepping	1 hr x 3/week	20 weeks	SpKt/V Six-minute Walk @ Wk10 Six-minute Walk @ Wk20	↑ 11% ↑ 14%, ↑14%	<0.05 <0.05 <0.05
Sakkas et al. (2003)	9	ESRD	Aerobic	IDT; cycling	Progressive to 40 minutes at 90% of VT	6 mths	Mean cross-section fibre area	↑46	<0.01
Storer et al. (2005)	12	HD	Aerobic	IDT; recumbent cycling	Progressive: 20 to 40 minutes at 30% or peak work rate	8.6 ± 2.3 weeks	Stair climbing Timed up-and-go (10m) Walking speed VO_2peak	↑ 22 ± 25% ↓12 ± 12 % ↑ 19 ± 16 % ↑22 ± 20 %	<0.05 <0.05 <0.01 <0.05

Suh et al. (2002)	14	HD	Aerobic	NDT; leg bicycling, treadmill or arm cycling	1 hr x 3/week	12 weeks	VO_2max Exercise duration Score of anxiety Depression Score of quality of life	↑13% ↑ 26 ↓ 12% ↓ 13% ↑ 7%	≤0.01 <0.01 <0.01 >0.05 <0.05
Toussaint et al. (2008)	19	Cross-over design	Aerobic	IDT; recumbent cycling	30 mins x 3/week of stationary bicycling at self-prescribed intensity	3 mths	PWV (group A) PWV (group B) PWV Combined (after exercise) B-type natriuretic peptide	↓ 16% ↓ 11% ↓ 11% ↓ 38%	>0.05 >0.05 <0.01 <0.05
Van Vilsteren et al. (2005)	96	RCT	Aerobic and resistance	Predialysis strength training and IDT cycling	20-30 mins x 2-3/week at RPE of 12	12 weeks	Manual dexterity (s) Reaction time (ms) Muscle strength (s) VO2 peak (ml.kg.min^{-1})	↓ 6% ↓ 11% ↓ 22% ↑ 10%	>0.05 <0.01 <0.05 >0.05

Data presented as percentage increase (↑) or decrease (↓). ESRD = End-stage renal disease, HD = haemodialysis, NDT = non-dialysis training, IDT – intradialytic training, RCT – randomised controlled trial, HR = heart rate, SpKt/V – single pooled urea clearance, VO_2max = Maximal oxygen consumption, PWA = Pulse wave analysis, PWV = Pulse wave velocity, RPE = Rating of Perceived Exertion, VT = ventilatory threshold.

To date exercise studies have been conducted in ESRD patients with varying degrees of positive reports (Kouidi et al., 1998, Van Vilsteren et al., 2005, Deligiannis et al., 1999). Exercise training during and outside dialysis have both been reported to result in significant positive effects on patients' physical (Kouidi et al., 2004, Storer et al., 2005) and mental health (Ouzouni et al., 2009). However, with the already high costs relating to providing health and clinical care to ESRD patients, interventions involving exercise training during dialysis may be labour and hence resource intensive. Thus methods to encourage or support patients' physical activity participation outside dialysis should be explored.

2.6.1 Exercise Interventions in Improving Physical Function in ESRD

Low physical capacities and poor exercise tolerance are common in ESRD populations (Johansen et al., 2003, Robertson et al., 1990) which may contribute to lower physical activity levels amongst ESRD patients (Johansen et al., 2000, Allen and Gappmaier, 2001). The low physical tolerance coupled with low physical activity levels may lead to further deterioration and disability in ESRD populations (Tawney et al., 2003). Several exercise interventions have reported significant improvements in physical function following exercise training (Headley et al., 2002, Storer et al., 2005, Van Vilsteren et al., 2005). Headley et al. (2002) investigated the effects of a progressive resistance training protocol which included one to three sets of nine resistance exercise that trained the muscles of the upper and lower limbs' as well as the abdominals. Ten haemodialysis patients trained at intensities that were equivalent to 15 on the Borg 6-20 RPE scale. The patients were also given stretch cords and were requested to use these once a week at home while following instructions in an exercise video. This unsupervised component was also made progressive by providing participants with higher resistance therabands midway through the intervention. Following the resistance training intervention, peak torque of the quadriceps muscles increased by 12.7% ($p<0.05$). Physical capacity and muscular endurance measured using the six-minute walk test also increased significantly by 5% ($p<0.05$). Improvements of

12.5% to 13.9% ($p<0.05$) were also reported in the sit-to-stand test however there was no change in grip strength. These significant improvements were made despite the limitation of the Borg scale being a subjective measure of exertion. Storer et al. (2005) studied the effects of 8.6 ± 2.3 weeks of progressive intradialytic training on semi recumbent cycle ergometers on measures of muscle fitness in twelve haemodialysis patients using an interval type training protocol where the work-rest ratio was 4:1. By the end of the intervention, participants were able to tolerate 40 minutes of training at an average 46% increase in work rate (29 ± 25 w). Average VO_2peak increased by 22% ($p<0.018$), peak work rate increased by 37% ($p=0.007$), and muscle endurance as measured using a bilateral leg press was significantly increased by 144 ± 170% ($p=0.0001$). In addition time to complete a stair climbing test improved by 15% from 2.24s to 1.91s ($p=0.030$), maximal walking speed increased by 19% from 164 to 194 $cm.s^{-1}$ ($p=0.003$) and timed-get up and go test improved by 12% from 7.6s to 6.5s ($p=0.012$). Van Vilsteren et al. (Van Vilsteren et al., 2005) studied a group of 96 haemodialysis patients randomly allocated to either usual care or a predialysis resistance training intervention training at intensities of 12 to 16 on the Borg 6-20 RPE scale, followed by intradialytic cycling, two to three times per week for 12 weeks. Compared to the control group, there was a significant improvement in the intervention group whose sit-to stand test improved ($p=0.05$) from 26.3 ± 14.6s to 20.4 ± 7.5s compared to 31.6 ± 19.7s to 31.6 ± 19.8s in the control group. Also, compared to the control group, the intervention group's reaction time decreased significantly ($p=0.02$) from 235 ± 44ms to 209 ± 36ms compared to that of the control group (249 ± 74ms to 255 ± 97ms). Exercise training may also prevent uremic muscle atrophy (Johansen et al., 2003) which is common in ESRD patients (Kouidi et al., 1998, Sakkas et al., 2003). Kouidi et al. (1998) and Sakkas et al. (2003) both reported significant increases in muscle fibre cross-sectional areas, oxidative areas and contractile areas, which correlates with the increases in physical function following exercise training in ESRD patients. Hence, these studies show that exercise intervention in various forms such as resistance training undertaken pre-dialysis or cycling training undertaken intradialysis have significant impact on haemodialysis patients' physical function.

2.6.2 Exercise Interventions in the Management of Cardiovascular Health in ESRD

It is well-known that exercise improves cardiovascular function in healthy populations. Exercise intervention studies in ESRD have also found promising results. Studies that examined cardiovascular changes with exercise interventions in kidney diseases found significant improvements in blood pressure regulation, heart rate variability, and left ventricular function (Deligiannis et al., 1999). It appears that intensity of exercise plays an important role in eliciting cardiovascular improvements. Deligiannis et al. (1999) compared the cardiovascular benefits of two different exercise intensities in 38 haemodialysis patients. Resting heart rate, systolic blood pressure, diastolic blood pressure, VO_{2max} and lactic acid removal significantly improved in the group that followed an outpatient exercise program which included a 10-minute warm up, 50-minutes of callisthenics, stepping, and flexibility exercises, and a low-resistance weight training program. This group trained three times per week for 90 minutes each session at 60-70% of HR_{max}. The group that followed a home-based moderate-intensity exercise program where they exercised 30 minutes at 50-60% of HR_{max} using a cycle ergometer 5 times a week had smaller but still significant improvements. In addition, while the high-intensity group had improvements in resting Stroke Volume Index (SVI), the moderate-intensity group did not.

As previously described (p.9), ESRD patients exhibit greater levels of arterial stiffness due to chronic fluid overload, biochemical imbalances of calcium and phosphate, and uraemia. Accelerated arterial stiffness increases cardiovascular morbidity and mortality. However, only two studies examining the effects of exercise training on arterial stiffness in haemodialysis patients have been published (Mustata et al., 2004, Toussaint et al., 2008b).

Both studies investigated the effects of exercise on arterial stiffness measured by applanation tonometry.

In an uncontrolled study Mustata et al. (2004), aerobically trained eleven haemodialysis patients for one hour, twice a week for three months. The heart rates recorded at peak exercise intensity of their participants during the twice weekly sessions were within an exercise physiologist prescribed target heart rate zone which were 134% of participants' mean pre-exercise heart rate values of 79 ± 6 bpm. Since Mustata et al. (2004) did not report the average training heart rates, it may be estimated from the pre-exercise heart rate values of 79 ± 6 bpm that their participants trained between 98 between 114 bpm, which based on the reported mean age of the group, correlated to approximately 68% of the group's predicted maximal heart rate: 220 bpm – age (years). While the exercise intensity based on the percentage of predicted maximum heart rate appears to be aerobic, the three-month exercise protocol was described as an out-patient program that consisted of a five- to ten-minute warm up followed by fifty-minutes of conditioning exercises, which concluded with a five- to ten-minute cool down. Following three-months of the exercise training, arterial stiffness i.e. augmentation index was reported to significantly decrease ($p<0.001$) from 17 ± 3 to 12 ± 3 arbitrary units.

Toussaint et al. (2008) performed a similar prospective study where nineteen haemodialysis subjects were randomised to either three-months of intradialytic aerobic exercise on recumbent bicycles followed by three-months of no training, or the same interventions in the reverse order using a cross-over study design. All participants performed the intradialytic cycling at a self-selected (i.e. not prescribed) intensity using participants' individual perceived levels of exertion; however, the average work performed per training session was approximately 70 kcal. When analysed as a whole following the completion of the cross-over, the arterial stiffness results of both groups were found to have reduced significantly following the exercise training intervention (aortic PWV: 9.04 ± 0.59 vs. 10.16 ± 0.74 ms^{-2}; $p=0.008$).

Interestingly, exercise-induced improvements in arterial stiffness in the above studies (Mustata et al., 2004, Toussaint et al., 2008b) albeit significant, were suggested to be transient. Both studies reported that after one month of cessation of the respective exercise protocols, arterial stiffness reverted to values that were comparable to those recorded at baseline. Another interesting comparison between the two studies unveils the conflicting evidence correlating arterial stiffness and pulse pressures. While Mustata et al. (2004) found that pulse pressures decreased in a similar manner to arterial stiffness following their exercise intervention, Toussaint et al. (2008b) reported that the changes in arterial stiffness in response to their training intervention did not correlate with changes in either blood pressure or pulse pressure.

2.6.3 The Effects of Exercise on Self-reported Health amongst Haemodialysis Patients

Exercise interventions have been found to benefit patients' perceptions of health and therefore their HRQoL outcomes (Ouzouni et al., 2009). Significant improvements in the physical component scale ($p<0.05$) of the SF-36 but not the mental component scale were found following a 10-month intradialytic exercise intervention (Ouzouni et al., 2009). In that randomised controlled study (Ouzouni et al., 2009), the intervention participants trained for 60-90 minutes per session three times per week which included 30 minutes of cycling, which was progressively increased to 60 minutes over the course of the study, and 30 minutes of strengthening and flexibility exercises. Endpoint values of the physical component scale were significantly elevated ($p<0.05$) when comparing the intervention group with the control group. In addition there were significant decreases in depression following the intervention in the intervention group (Ouzouni et al., 2009).

2.7 Summary

This literature review has discussed the elevated mortality rates and high incidence of co-morbidities in ESRD populations. The negative effects of ESRD on arterial stiffness, physical function and HRQoL are evident in the relationships established with these parameters: cardiovascular comorbidities are closely linked to arterial stiffness; low physical functioning is reflected in the poor performances on functional tests; and finally, HRQoL decreases with time spent on haemodialysis. However, studies investigating the potential benefits of exercise training have reported improvements in cardiovascular function, physical capacities and self-reported HRQoL irrespective of whether the exercise was intradialytic or outside dialysis, or whether it was supervised or unsupervised. There is some evidence supporting the role of supervised exercise as a therapeutic agent in lowering arterial stiffness however the effect of unsupervised home-based exercise on arterial stiffness has not yet been investigated. There may be merit in such an investigation into the effectiveness of this cost-efficient method of exercise prescription in improving arterial compliance, physical function and HRQoL.

The primary purpose of this study was to investigate the effect of intradialytic and home based exercise training on arterial stiffness in ESRD. A secondary purpose was to explore the effects of an unsupervised walking program on patients' physical function. Finally, a third purpose was to determine the effects of exercise training on patients' perceptions of their health and quality of life.

CHAPTER 3

METHODS

3.1 Study Design and Setting

This study in haemodialysis patients was a multi-centre, randomised controlled trial conducted at the Launceston General Hospital, the Burnie Satellite Renal Unit in Northern Tasmania and the Hobart Renal Unit, which, combined, service a population of approximately 485,000.

3.2 Participants

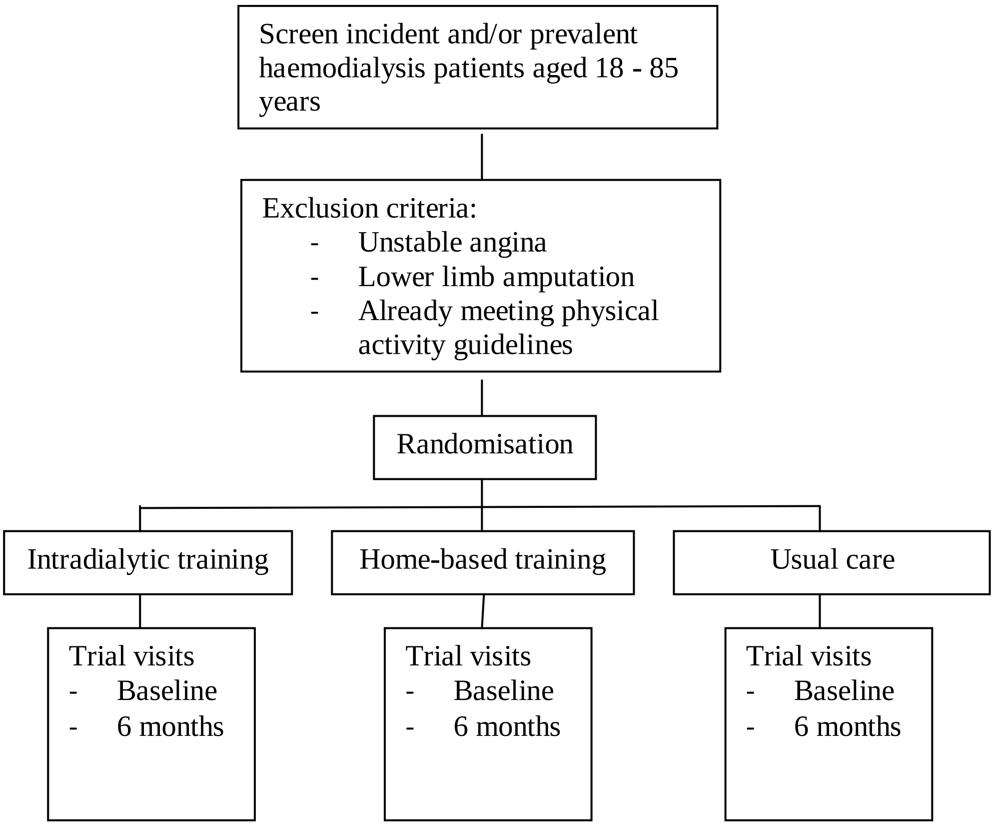

Figure 3.1. Flow of Participants throughout the study

Haemodialysis patients aged 18 to 85 years who had commenced and/or maintained stable dialysis for at least three months prior to the start of the study were approached to participate in the present study. Eligible patients received a copy of the patient information sheet and the principal investigator explained the study during a medical consultation. Following the consultation the patient was asked to take the information sheet home for consideration and to make a decision before their next haemodialysis visit. If at the next haemodialysis visit patients agreed to participate in the study, they would sign the consent form with an independent person signing as witness. Once consented, participants were randomised to intradialytic exercise training, home-based walking or usual care group. This randomisation was performed by an independent person not associated with the trial using a computer generated random number system (Fig. 2). Detailed information on sample size at each stage of the study is presented in Figure 4.1 (p. 46)

3.3 Eligibility

Incident and prevalent haemodialysis patients who met the inclusion criteria: 18 and 85 years of age and maintained stable adequate haemodialysis with urea reduction ratio of at least 70% for at least three months were eligible for this study. Patients were excluded if they presented with unstable angina, lower limb amputation or if they already met or exceeded the recommended amount of 120 minutes of moderate intensity physical activity per week (US Department of Health and Human Services, 1996). Patients were also excluded if they were participating in, or proposed to participate in, another clinical intervention within 30 days prior to study entry.

The study was approved by the Tasmania Statewide Scientific and Ethics Committees (Appendix B). A condition of ethical approval required investigators to provide brochures to all haemodialysis patients at each study site indicating the benefits of regular exercise. Participants were withdrawn from the study at their request, without prejudice, as documented and explained at the time of consenting. This study was also registered with the Australian New Zealand Clinical Trials Registry (ACTRN12608000247370).

3.4 Interventions

Intradialytic (ID) training required participants to train on cycle ergometer (Rehab Trainer 881E, Monark™, Sweden) within the first two hours of each dialysis session, three times per week for six months. Training intensity was individualised on the basis of perceived exertion, exercise heart rate and blood pressure. Participants were requested to exercise at an RPE of 12-13 on the Borg 6-20 scale (Borg, 1998). In cases where participants' heart rates were low at their reported RPE of 12-13, the exercise supervisor increased the resistance to elicit a greater cardiorespiratory response. However, participants were allowed to stop and rest or request to exercise at a lower intensity. When blood pressure exceeded predetermined safe levels (>200/110 mmHg), the exercise was halted and blood pressure was monitored until it returned to safe levels (<180/110 mmHg). Participants taking medications that affect cardiac sinus rhythm were trained strictly according to RPE. Over the duration of the study, the resistance of the ergometer was periodically increased to maintain RPE. Participants were encouraged to start and progress the duration of the exercise according to their individual abilities, however, a general guideline was used to encourage participants to complete at least 15 minutes of exercise per session in the first two weeks of the intervention. This duration was increased weekly until participants exercised for 30 minutes per session by week 12 and to 45 minutes by week 24. Power output (W) and duration of exercise (minutes) of each exercise session was recorded to estimate participants' individual energy expenditure per session during the training period.

Participants randomised to home-based (HB) training were provided with pedometers and asked to perform thrice-weekly unsupervised walking for six months at perceived exertions of 12-13 on the Borg 6-20 scale. To ensure similar treatment to the intradialytic group's training duration, HB participants were requested to start and progress their walking programme according to individual capabilities; however, investigators encouraged participants to start at 15 minutes per session for the first two weeks and to increase duration to 30 minutes by week 12 and to 45 minutes by week 24 as per ID group. HB participants were phoned every fortnight to provide encouragement and feedback. HB participants were also encouraged to increase the intensity by walking faster or walking on routes with some degree of incline. The two exercise interventions were very different in nature; however, it was a challenge to administer either intervention exclusively because patients were limited in the amount of movement they could make whilst undergoing haemodialysis treatment; hence, walking was not feasible during haemodialysis. Moreover, cycling outside of dialysis posed other challenges such as additional travelling to a fitness centre and the added manpower involved if this path was taken. The comparison of two different modes of exercise presents was not ideal and presents as a limitation in the methodology of the present study despite the study's efforts to control the intensity of the intervention programmes.

Usual care (UC) participants were requested to maintain their usual daily activities and were reminded of the importance of this regularly throughout the study. A condition of ethical approval required investigators to provide brochures about exercise benefits to all patients regardless of their decision to participate or to which group they were allocated. Adherence to exercise training was assessed by auditing training diaries. The supervisors completed the ID participants' diaries while HB participants completed the diaries themselves and returned them at the testing session.

3.5 Outcome Measures

Once randomised, participants underwent a series of tests of physical function and arterial stiffness and answered questionnaires to indicate self reported health at baseline and six months. The same researcher conducted all tests and analyses for each participant at both time points. All participants were instructed to refrain from physical activity for 24 hours and food and caffeine intake for three hours prior to each testing session.

3.6 Physical Function Tests

Physical function was assessed using the 6-minute walk test (6MWT), timed-up and go (TUG) and grip strength tests. The 6MWT was performed along a 25-metre stretch of walkway in a quiet hospital corridor. Prior to the test, participants underwent a short warm up and familiarisation with the walkway, which was marked with two lines at each end indicating the start and end of the 25-metre course. A chair was placed in the middle of the walkway in the event that participants required a rest. Subjects were instructed to walk as fast as they could manage for six minutes and they were allowed to stop and rest if needed. All participants received regular encouragement from the investigator throughout the test such as “two minutes now, you are doing well” and “well done, it is four minutes now, keep going!” Participants, but not investigators, were blinded to the previous test results.

Following the 6MWT, participants’ mobility was assessed with the Timed-Up & Go (TUG) test. A standard hospital chair, made of plastic and metal, of approximate height of 44cm from the ground to the top of the seat, and without arm rests was placed behind a marker indicating 0-metre. Another marker was placed at 3-metres in front of the chair. Participants were instructed to start by sitting with their backs fully resting on the back of the chair and at the word, “Go!” stand without using their arms for support, walk up to the 3-metre mark before turning around to return to the original sitting position. The time taken, in seconds (s), for participants to stand from a seated position, walk 3-metres, turn, and walk back to a chair, and return to the seated position was recorded. Time was taken the moment participants planted their feet firmly on the ground to get up to the time the participants' backs were fully touching the back of the chair. The better of two attempts was recorded as the final result.

Grip strength of the dominant arm was measured using a handgrip dynamometer (Smedleys™, TTM, www.stoeltingco.com). The distance between the handle and the lever was set at 60 mm for men and 55 mm for women. Patients first stood comfortably with their feet approximately shoulder width apart and held the dynamometer with their dominant hand with a nearly straight elbow above the shoulder. They were instructed to squeeze on the lever as hard as possible while, at the same time, bring the hand down to their side. Participants were given 2 attempts, and the highest force (kg) was recorded.

3.7 Blood Pressure Measurement

Arterial stiffness measures were obtained at the same time of day in the hour preceding dialysis in a quiet temperature controlled room (approximately 25°C) to ensure that diurnal variations in PWV were minimized. Brachial blood pressure was measured using a standard automated sphygmomanometer (A&D Digital Blood Pressure Machine, UA-767, A&D, Saitama, Japan). Participants rested in a supine position on a bed for five minutes prior to the commencement of the arterial stiffness measurements. At the end of the rest period two measurements of brachial blood pressure were taken approximately taken two minutes apart (UA-767, A&D, Saitama, Japan).

3.7.1 Pulse Wave Analysis

The average systolic and diastolic blood pressures of the two brachial blood pressure measurements were calculated and the resultant blood pressure was entered into the SphygmoCor™ programme prior to the measurement of pulse wave analysis (PWA) for the calculation of central pulse pressures, augmentation and other arterial stiffness parameters. Pulse wave analysis was performed on participants' non-fistula wrist where the radial pulse may be palpated. An 'X' was drawn on the wrist where the strongest pulse may be palpated. In participants with a fistula or arterial grafts in both arms, the brachial pulse on the brachial artery (medial to biceps) of the dominant arm was used. A pencil-shaped high-fidelity tonometer (SPT-301 Mikro-Tip; Millar Instruments, www.millarinstruments. com), was then placed on the radial artery for approximately one minute to collect 11 seconds or approximately 10 cycles of the radial pulse pressure waveforms to generate an averaged peripheral and corresponding central (aortic) waveform. Recordings were regarded as satisfactory if the variation in the systolic peaks and diastolic nadir were 5% or less and the operator index scored more than 85; recordings with more than 5% variation and/or under an operator index of 85 were discarded and re-measured. Central blood pressures and AIx were estimated from the obtained waveforms using customized software (SphygmorCor 7.01) with a validated (Chen et al., 1997) and reproducible (Frimodt-Moller et al., 2008) generalized transfer function. Augmentation Index (AIx)was defined as the difference between the 2nd and 1st central systolic peaks expressed as a percentage of central pulse pressure (Murgo et al., 1980). Since heart rate has an effect on AIx, the SphygmoCor software also incorporates an algorithm which adjusts AIx to a standard heart rate of 75 beats per minute (bpm) (Wilkinson et al., 2000).

3.7.2 Pulse Wave Velocity

Peripheral and aortic pulse wave velocities were two primary outcome measures in the present thesis. Similar to the pulse wave analysis, this method involved an electrocardiogram (ECG)-gated sequential applanation tonometry (SPT-301 Mikro-Tip; Millar Instruments, www.millarinstruments.com) of the common carotid, radial and femoral arteries using the foot-to-foot method which was guided by the SphygmoCor™ Software programme (SphygmoCor 7.01; AtCor Medical, Sydney, Australia;

www.atcormedical.com) as previously described (Wilkinson et al., 1998). Briefly, the three electrodes were placed on the chest at the right clavicle next to the suprasternal notch (Right Arm), the xyphoid process (Left Leg) and on the 6th rib along and slightly anterior to the left axillary line (Left Arm). Next, another 'X' was drawn on the lateral side of the neck where the strongest pulse could be felt on the common carotid artery. The distance between the suprasternal notch to the 'X' on the carotid artery was measured (in millimetres) using a standard anthropometry compatible measuring tape and recorded as the *proximal distance* as required by the SphygmoCor™ programme. The *distal distance* was measured (mm) from the suprasternal notch to the glenohumeral joint and finally, following the brachial artery (medial to biceps), to the 'X' marked on the wrist. The proximal and distal distances were required for the calculation for peripheral pulse wave velocity over a known length of vasculature i.e. of the upper limb in this case. A final 'X' was drawn on the site of the femoral artery where the femoral pulse was palpated (next to the groin). The distance from the suprasternal notch to the 'X' on the femoral artery was measured and recorded as the distal distance for the measurement of the aortic pulse wave velocity (carotid-femoral). Peripheral pulse wave velocity (carotid-radial) and aortic pulse wave velocity (carotid-femoral) were assessed using the foot-to-foot method where the R-intervals on the ECG waveforms indicated the time of each ventricular systole and the corresponding 'foot' of the pulse pressure waveforms indicated the time where pressure exerted from each ventricular systole reached the pulse site, thereby allowing for the calculation of the velocity of the pressure wave (Fig. 1). Pulse wave velocity measurements were regarded as satisfactory if recordings were within 2 S.D. of the mean (Nichols, 2005).

3.8 Self-Reported Health and Weekly Physical Activity Levels

Participants' perceived health status was evaluated using the Medical Outcomes Short-Form 36-Items (SF-36) Health Survey (Ware et al., 1997) (Appendix C). Widely used in HD populations previously (Painter et al., 2000, Knight et al., 2003), it includes 36 questions across eight independent scales: physical functioning (PF), role functioning/ physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role functioning/ emotional (RE), and mental health (MH) which assess physical and mental dimensions of health. Questions in each scale are scored from 0 to 100, with 100 being the highest possible score, or best possible health (Ware et al., 1997). The SF-36 was self-administered while participants were at one of their designated dialysis sessions, with the interviewer providing clarification and interpreting questions where necessary.

Participants' weekly physical activity was assessed with a validated (Johansen et al., 2001) questionnaire- Active Australia (AA) Questionnaire (Ware et al., 1997). This questionnaire assessed weekly time (minutes) spent walking, performing gardening duties, and participating in vigorous, moderate and light intensity activities. (Appendix D) Participants in the exercise groups were asked to include any training performed in the previous week as part of the study in their response to the questionnaire. The questionnaire measures frequency, intensity and duration of incidental and/or intentional physical activity in the week prior to the time of testing. The total time spent in each activity was multiplied by an intensity value (3.5 [light], 4 [moderate] and 7 [vigorous]) and used to calculate participants' weekly physical activity in MET.min^{-1}. To elicit any health promoting benefits, at least 600 MET.min^{-1} must be fulfilled each week. The AA Questionnaire was also self-administered during the same dialysis session when the SF-36 was administered, with the interviewer providing clarification where necessary.

3.9 Sample Size Calculation

Data from other studies indicates that the 6MWT has the highest variability of the two primary outcome measures (mean ± SD; PWV = 11.1 ± 3.2 ms^{-2} (London et al., 1990), 6MWT = 347 ± 147 m (Painter et al., 2000)). The present study assumed that this meant that changes in the 6MWT would be more variable than the changes in PWV. It was then assumed that a 10% improvement in the 6MWT would be clinically significant. Therefore, with alpha = 0.05 and beta = (1-0.1 = 0.9), the present study required 17 participants per group to achieve significant differences. Allowing for a 20% withdrawal rate, we aimed to recruit 20 participants per randomisation group.

3.10 Statistical Analyses

All statistical analyses were performed using STATA statistical software (STATA 10; Statistical data analysis; Stata Corp; College Station; Texas, USA). Baseline categorical data was compared using logistic regression and baseline continuous data using one-way ANOVA. Comparison of descriptive variables for completers and non-completers was performed using t-tests. Parametric longitudinal data were compared using generalized estimating equation (GEE) models corrected for repeated measures. Results were expressed as means and standard deviation (SD), and the mean difference (ANOVA with 95% confidence intervals) in change from baseline to end of treatment in the ID and HB groups was compared to the UC group. Weekly physical activity ($MET.min^{-1}$/week) was analyzed as Box-Cox-transformed values in the GEE models due to skewed distribution of residual values (using Cameron & Trivedi's information matrix test) when untransformed values were used. P-values were adjusted for multiple comparisons where appropriate using the Holm test. Statistical significance was set at $p < 0.05$.

CHAPTER 4

RESULTS

4.1 Patient Characteristics

Of 113 consecutive patients across the three renal units that were approached, 70 consented and were randomly assigned to receive either intradialytic exercise (n = 27), home-based exercise (n = 21), or usual care (n = 22). Patient flow through the study, including reasons for withdrawal, is shown in Fig 4.1. Forty-six haemodialysis (HD) participants (29 men; mean age, 51.9 ± 12.8 years; mean body mass index (BMI), 27.4 ± 8.0 kg/m2; mean time on HD therapy, 30.5 ± 26.6 months) completed the study and descriptive data for each intervention group is presented in Table 4.1. No significant differences were found in any descriptive variable (Table 4.1.) or medication use (Table 4.2) between groups at baseline. There were no significant differences in baseline descriptive variables between participants who completed the study and those who withdrew.

Exercise training adherence between the intradialytic exercise (75% ± 19%) and home-based exercise (71% ± 13%) groups was similar (p = 0.9). Intradialytic-exercise participants reported vascular access stability issues, tiredness, and dialysis-related hypotension as the main reasons for not training, whereas home-based-exercise participants reported fatigue, post dialysis hypotension, heart palpitations, and work commitments as reasons for missing walking sessions. No intervention-related serious adverse events were reported.

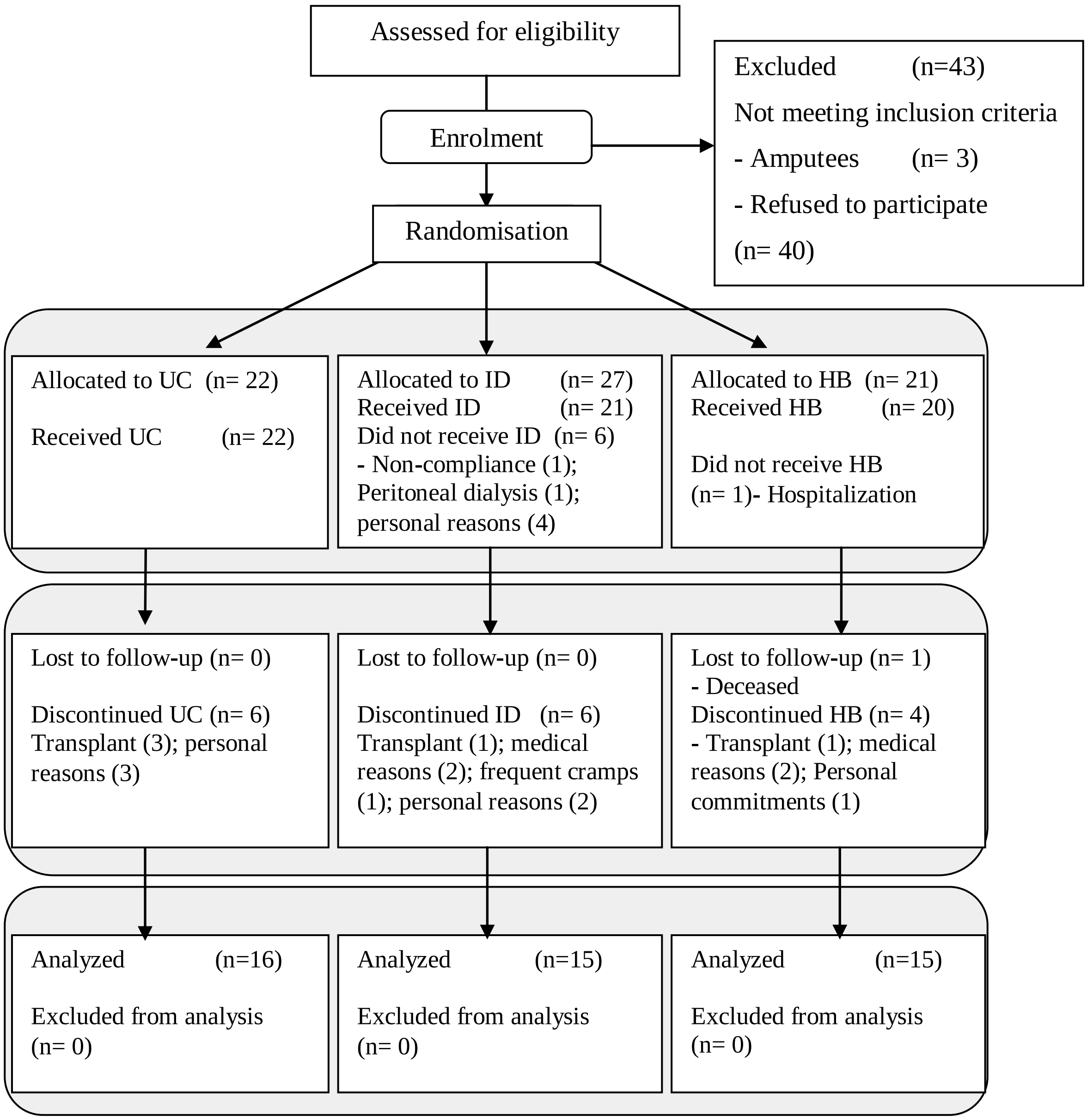

Figure 4.1 Flow diagram depicting study progress from assessment of eligibility to data analysis. Abbreviations: UC, usual care; ID, intradialytic training; HB, home-based training.

Table 4.1 Descriptive Data of Participants at Baseline

	UC	ID	HB	Total
Age (years)	51.3 (14.4)	52.3(10.9)	52.1 (13.6)	51.9 (12.8)
Sex (Men/Women)	8 / 8	10 / 5	11 / 4	29/17
Height (cm)	167 (8)	167 (8)	169 (11)	168 (9)
Weight (kg)	80.8 (25.2)	75.9(13.9)	80.7 (19.1)	79.1 (19.8)
Body Mass Index	28.6 (7.3)	27.6 (7.2)	27.9 (4.9)	28.1 (6.5)
Resting SBP (mmHg)	145 (18)	148 (22)	143 (32)	145 (24)
Resting DBP (mmHg)	80 (9)	82 (10)	78 (16)	80 (12)
COMORBIDITIES				
Hypertension	11	10	8	29
Essential Hypertension	2	5	3	10
Isolated Systolic Hypertension	9	5	5	19
Diabetes (Type I / Type II)	(0/2)	(0/1)	(1/1)	(1/4)
Other CVD (n=13)	3	3	7	13
Prior Myocardial Infarction	0	0	2	2
Cardiac Procedure	2	0	3	5
Angina	1	1	1	3
Mitral Regurgitation	0	1	0	1
Other Arterial disease	0	1	1	2
Length of ESRD (months)	25.8 (22.2)	32.1(26.7)	37.0 (31.1)	32.0 (27.8)

Data presented as mean (SD); ESRD-ESRD.

Table 4.2.Participants' Prescribed Medication at Baseline

Medication List	UC (n=16)	ID (n=15)	HB (n=15)
Antihypertensives	6	8	6
Diuretic	4	2	3
Hypolipidaemic Agents	3	3	5
Anticoagulants	4	2	3
Bone and Calcium Agents	10	14	9
Haematopoietic Agents	12	14	10

4.2 Physical Function and Physical Activity

There were no significant differences in 6MWT (*P* = 0.6) between groups at baseline (Table 5.). Compared with usual care, there were no significant changes in 6MWT (intradialytic exercise, +14%, *P* = 0.2; home-based exercise, +11%, *P* = 0.3; observed power, 0.41).

No differences were observed between groups for TUG (*P* = 0.7) or grip strength (*P* = 0.3) at baseline. Compared with usual care, no treatment effect was observed for either TUG or grip strength during the 6-month period (Table 4.3). No differences in weekly physical activity (MET.min^{-1}.wk^{-1}; p = 0.9) were observed between groups at baseline. Self reported physical activity increased significantly in the intradialytic exercise group (p = 0.03), but not in the home-based-exercise group (p = 0.3; Table 4.3).

Table 4.3. Effects of HB or ID Exercise Training and Usual Care on Physical Function and Weekly Physical Activity

	n	Baseline Mean (SD)	End Mean (SD)	Comparison of ID and HB with UC[1] Difference in change	95% CI	P-value[2]
6-MINUTE WALK (m)						
Usual care	16	431 (160)	452 (144)	0		
Intradialytic	14	463 (127)	526 (97)	42.3	(-6.5 to 91.0)	0.2
Home based	14	444 (127)	493 (143)	27.6	(-21.2 to 76.3)	0.3
GRIP STRENGTH (kg)						
Usual care	12	28.5 (13.4)	31.3 (12.1)	0		
Intradialytic	14	34.4 (10.0)	34.7 (10.9)	-2	(-5.6 to 2.0)	0.7
Home based	11	32.4 (13.5)	34.5 (12.9)	-2	(-4.3 to 3.4)	0.8
TIMED UP & GO(s)						
Usual care	12	6.41 (2.59)	6.16 (1.50)	0		
Intradialytic	14	5.79 (1.48)	5.27 (1.46)	-0.3	(-1.39 to 0.77)	0.9
Home based	11	6.05 (1.91)	5.97 (2.19)	+0.3	(-0.84 to 1.36)	0.6
WEEKLY PHYSICAL ACTIVITY (MET.min^{-1}.week^{-1})[3]						
Usual care	15	692 (771)	943 (1,701)	0		
Intradialytic	15	528 (795)	1,920 (3,273)	6.42	(1.47 to 28.08)	0.03
Home based	15	848 (1,470)	1,712 (3,868)	1.84	(0.69 to 5.48)	0.3

1 The mean difference in change in exercise levels between baseline and end of treatment of inpatient and home care groups was estimated using generalized estimating equation (GEE) models, corrected for repeated measures

2 P-values were corrected for multiple comparisons by the Holm method

3 Weekly physical activity was expressed as untransformed values for mean and standard deviation, but as a Box-Cox transformation in the GEE models due to skewed distribution of residual values when untransformed values were used

4.3 Self-Reported Health

No statistically significant differences were observed between groups in any SF-36 score at baseline (p =0.9; Table 4.4). Compared with usual care, physical function decreased significantly in the intradialytic exercise group (-25%; p = 0.01) and was unchanged in the home-based-exercise group (+5%; p = 0.6; Table 4.4). No significant changes were observed following the intervention in any other SF-36 score.

Table 4.4 Effects of HB or ID Exercise Training and Usual Care on Self Reported Health

		Baseline	End	Comparison of ID and HB with UC[1]		
	N	Mean (SD)	Mean (SD)	Difference in change	95% CI	P-value[2]
PHYSICAL FUNCTION						
Usual care	15	63 (34)	70 (26)	0		
Intradialytic	15	68 (24)	58 (23)	-17	(-27.8 to -5.5)	0.01
Home based	15	66 (23)	77 (24)	3	(-7.8 to 14.5)	0.6
ROLE PHYSICAL						
Usual care	15	60 (58)	48 (44)	0		
Intradialytic	15	38 (43)	31 (42)	5	(-27.1 to 37.1)	0.8
Home based	15	48 (42)	43 (38)	7	(-25.5 to 38.8)	0.9
BODILY PAIN						
Usual care	15	59 (49)	57 (31)	0		
Intradialytic	15	71 (27)	58 (27)	-11	(-34.6 to 12.5)	0.4
Home based	15	50 (29)	67 (33)	19	(-4.7 to 42.3)	0.2
GENERAL HEALTH						
Usual care	15	51 (32)	48 (27)	0		
Intradialytic	15	39 (20)	36 (21)	0	(-14.3 to 14.0)	0.9
Home based	15	38 (25)	42 (26)	7	(-7.6 to 20.8)	0.7
VITALITY						
Usual care	15	56 (25)	52 (23)	0		
Intradialytic	15	51 (26)	49 (21)	2	(-10.0 to 13.4)	0.8
Home based	15	50 (22)	53 (26)	7	(-4.4 to 19.0)	0.4
SOCIAL FUNCTION						
Usual care	15	82 (27)	73 (30)	0		
Intradialytic	15	74 (25)	67 (23)	1	(-16.6 to 18.3)	0.9
Home based	15	79 (23)	70 (32)	0	(-17.6 to 17.3)	0.9
ROLE EMOTIONAL						
Usual care	15	69 (43)	69 (41)	0		
Intradialytic	15	60 (48)	64 (46)	4	(-22.4 to 31.1)	0.8
Home based	15	60 (46)	84 (35)	24	(-2.4 to 51.1)	0.1
MENTAL HEALTH						

Usual care	15	73 (25)	77 (16)			
Intradialytic	15	77 (19)	73 (16)	-8	(-17.2 to 1.2)	0.2
Home based	15	71 (19)	76 (16)	1	(-8.4 to 10.0)	0.9
PHYSICAL COMPONENT SCORE						
Usual care	15	55 (29)	55 (25)			
Intradialytic	15	53 (22)	47 (20)	-7	(-19.4 to 5.8)	0.6
Home based	15	50 (23)	56 (25)	6	(-6.8 to 18.5)	0.4
MENTAL COMPONENT SCORE						
Usual care	15	66 (26)	64 (25)			
Intradialytic	15	60 (22)	58 (20)	0	(-9.4 to 9.2)	0.9
Home based	15	59 (22)	65 (22)	8	(-1.4 to 17.2)	0.2

[1] The mean difference in change in exercise levels between baseline and end of treatment of inpatient and home care groups was estimated using generalized estimating equation (GEE) models, corrected for repeated measures

[2] P-values were corrected for multiple comparisons by the Holm method

4.4 Blood Pressure and Pulse Wave Velocity

There were no baseline differences between groups in central (systolic, p = 0.5; diastolic, p = 0.6) or peripheral (systolic, p = 0.9; diastolic, p = 0.6) blood pressures, augmentation index (AIx: p = 0.5), AIx at heart rate of 75 beats/min (p = 0.7), or aortic (p = 0.7) or peripheral (p = 0.6) PWV (Table 4.5). Compared with usual care, no treatment effect was observed for either aortic (intradialytic exercise, -0.8 $m.s^{-1}$, p = 0.4; home-based exercise, -0.7 $m.s^{-1}$, p = 0.3; observed power, 0.42) or peripheral (intradialytic exercise, -0.9 $m.s^{-1}$, p = 0.2; home-based exercise, -0.6 $m.s^{-1}$, p = 0.3; observed power, 0.23) PWV or any measure of central or peripheral blood pressure after the intervention (Table 4.5). When data were separated and analyzed on the basis of hypertension status at baseline, no treatment effects were observed in any measure of arterial health for those without high blood pressure or those with either essential or isolated systolic hypertension.

Table 4.5. Effects of HB or ID Exercise Training and Usual Care on Cardiovascular Parameters

	n	Baseline Mean (SD)	End Mean (SD)	Comparison of ID and HB with UC[1] Difference in change	95% CI	P-value[2]
HEART RATE *(bpm)*						
Usual care	16	74 (10)	75 (12)			
Intradialytic	15	70 (13)	69 (11)	-2	(-9.1 to 5.7)	0.7
Home based	15	73 (9)	71 (10)	-3	(-10.2 to 4.5)	0.9
PERIPHERAL SBP (mmHg)						
Usual care	16	145 (18)	136 (29)			
Intradialytic	15	148 (22)	139 (22)	0	(-17.1 to 17.7)	0.9
Home based	15	144 (32)	142 (29)	8	(-9.7 to 25.1)	0.8
PERIPHERAL DBP (mmHg)						
Usual care	16	80 (9)	75 (15)			
Intradialytic	15	83 (10)	77 (10)	-1	(-9.6 to 8.6)	0.9
Home based	15	78 (16)	79 (16)	6	(-2.8 to 15.3)	0.4
PERIPHERAL PP (mmHg)						
Usual care	16	65 (18)	61 (19)			
Intradialytic	15	65 (20)	62 (20)	1	(-9.9 to 11.7)	0.9
Home based	15	66 (20)	63 (18)	2	(-9.3 to 12.3)	0.9
CENTRAL SBP (mmHg)						
Usual care	16	129 (18)	122 (27)			
Intradialytic	15	137 (23)	129 (22)	-1	(-17.7 to 16.4)	0.9
Home based	15	129 (31)	129 (30)	7	(-10.1 to 24.0)	0.9
CENTRAL DBP (mmHg)						
Usual care	16	81 (10)	77 (16)			
Intradialytic	15	85 (11)	78 (11)	-1	(-10.6 to 8.1)	0.8
Home based	15	80 (16)	81 (17)	6	(-3.7 to 15.0)	0.5
CENTRAL PP (mmHg)						
Usual care	16	48 (14)	46 (15)			
Intradialytic	15	52 (21)	50 (20)	0	(-10.3 to 9.3)	0.9
Home based	15	49 (19)	49 (19)	1	(-9.2 to 10.4)	0.9
MAP (mmHg)						
Usual care	16	102 (13)	96 (21)			
Intradialytic	15	106 (14)	100 (13)	-1	(-13.9 to 11.6)	0.9

Home based	15	101 (21)	101 (21)	6	(-7.2 to 18.2)	0.8
EJECTION DURATION (ms)						
Usual care	16	322 (21)	324 (38)			
Intradialytic	15	333 (31)	334 (32)	0	(-23.1 to 22.3)	0.9
Home based	15	324 (19)	322 (41)	-4	(-26.5 to 19.0)	0.9
TIME TO REFLECTION (ms)						
Usual care	15	138 (13)	140 (17)			
Intradialytic	14	139 (8)	143 (15)	2	(-12.2 to 16.6)	0.8
Home based	15	141 (16)	150 (26)	8	(-6.5 to 21.9)	0.6
PULSE PRESSURE AMPLIFICATION						
Usual care	16	1.37 (0.21)	1.34 (0.23)			
Intradialytic	15	1.31 (0.21)	1.27 (0.16)	-0.01	(-0.14 to 0.12)	0.9
Home based	15	1.38 (0.23)	1.35 (0.21)	0	(-0.13 to 0.14)	0.9
P1 HEIGHT (mmHg)						
Usual care	16	36 (10)	34 (10)			
Intradialytic	15	37 (12)	36 (13)	1	(-5.0 to 7.5)	0.7
Home based	15	37 (11)	36 (10)	2	(-4.7 to 7.8)	0.9
AUGMENTATION (mmHg)						
Usual care	16	11.3 (9.9)	12.2 (8.7)			
Intradialytic	15	15.5 (10.6)	15.0 (9.8)	-1.3	(-6.75 to 4.07)	0.9
Home based	15	12.2 (11.6)	12.3 (11.9)	-0.8	(-6.22 to 4.60)	0.8
AIx (%)						
Usual care	16	22 (17)	24 (17)			
Intradialytic	15	27 (12)	28 (11)	-1	(-10.2 to 8.1)	0.8
Home based	15	21 (19)	19 (17)	-3	(-11.8 to 6.5)	0.9
AIx @ 75bpm (%)						
Usual care	16	22 (17)	24 (17)			
Intradialytic	15	24 (11)	25 (10)	-1	(-9.5 to 6.6)	0.7
Home based	15	20 (18)	19 (17)	-4	(-11.8 to 4.3)	0.7
PWV CENTRAL ($m.s^{-1}$)						
Usual care	15	8.7 (2.5)	9.2 (3.5)			
Intradialytic	13	9.1 (2.8)	8.8 (2.9)	-0.8	(-2.11 to 0.48)	0.4
Home based	14	9.7 (3.2)	9.5 (3.4)	-0.7	(-1.92 to 0.62)	0.3
PWV PERIPHERAL ($m.s^{-1}$)						
Usual care	16	8.0 (2.2)	8.7 (1.8)			
Intradialytic	15	8.6 (1.2)	8.3 (1.1)	-0.9	(-2.02 to 0.18)	0.2

Home based	15	8.3 (1.8)	8.4 (1.7)	-0.6	(-1.68 to 0.52)	0.3

[1] The mean difference in change in exercise levels between baseline and end of treatment of inpatient and home care groups was estimated using generalized estimating equation (GEE) models, corrected for repeated measures

[2] P-values were corrected for multiple comparisons by the Holm method

CHAPTER 5

DISCUSSION

5.1 Major Findings

Four major findings emerged from this study. First, neither form of training significantly improved 6-minute walk distance compared with usual care. Second, physical activity increased in the intradialytic-exercise group, but not in the home-based-exercise group. Third, self-reported physical function decreased significantly with intradialytic-exercise training. Finally, there were no changes in any of the measured vascular parameters. The following sections will discuss these findings in further detail.

5.2 Physical Function

The 6-minute walk distance improved by similar amounts after both intradialytic-exercise and home-based-exercise protocols, although the improvements were not statistically significant. However, given that low exercise capacity measured using peak oxygen consumption has been identified as a powerful predictor of mortality in patients with ESRD (Sietsema et al., 2004), the observed changes in 6-minute walk distance in both intervention groups may be clinically significant. However a larger study or longer duration intervention may be required to achieve statistical significance. Previously (Kouidi et al., 2004), peak oxygen consumption was reported to increase after one year of thrice-weekly intradialytic exercise training on stationary bicycles compared with a smaller, yet still significant, improvement after an outpatient program. In this previous study, the outpatient exercise program was supervised and included a combination of calisthenics, stepping, and flexibility, making it resource intensive and limiting the comparisons between it and the home-based exercise training used in the present study. In contrast, true comparisons of supervised versus unsupervised training have reported similar between-group improvements in exercise capacity in coronary artery bypass graft patients (Kodis et al., 2001), whereas a recent review (Bendermacher et al., 2006) indicates that supervised exercise results in greater improvements in walking distance than unsupervised exercise in patients with peripheral arterial disease.

A potential reason for the non-significant improvements observed in 6-minute walk distance in the current study may involve the volume or intensity of physical activity undertaken. Participants were requested to exercise at an intensity of 12-13 on the 6-20–point Borg RPE scale (Borg, 1982). While intradialytic-exercise participants were provided with feedback for exercise heart rate and blood pressure to ensure that appropriate training intensities were maintained, home-based-exercise participants trained with no supervision. As Borg RPE correlates with exercise heart rate through a range of relative exercise intensities (Borg, 1982), it was hypothesised that exercise intensity prescribed on the basis of the Borg RPE would be suitable for all patients. Nevertheless it is possible that fatigue and lack of motivation resulted in increased ratings of Borg RPE in both training groups. Although this would have been reflected in blunted training heart rates and blood pressures, which were not observed in the intradialytic-exercise group, a similar effect in the home-based-exercise group would have gone unobserved. This theory may be partially supported by the changes in self-reported physical activity. Although the increase in self-reported physical activity in the intradialytic-exercise group during the intervention period was significant, there was no statistically significant change in the home-based-exercise group (Table 4.3), indicating that the volume or intensity of training using home-based exercise may not have met the requested levels or that home-based-exercise participants reduced their involvement in non-prescribed physical activity during the intervention period. Although this provides a potential explanation for the lack of increase in the home-based exercise group, it also must be acknowledged that the lack of change in 6-minute walk distance may be caused by the mean increase in physical activity observed in the usual-care group, as well as the large variability in data.

No significant changes were observed in TUG in any group after the intervention. This result contrasts with those of Storer et al. (2005) who reported a statistically significant 12% increase in TUG performance ($p<0.012$) after a similar exercise training program to that used in the current study. Participants in Storer et al.'s (2005) study completed 18 weeks of recumbent cycling with initial duration of approximately 20 minutes at 19 ± 9 w, which was approximately 30% of their participants' measured peak work rate (66 ± 32 w) at baseline. After progressive increases in workload over the 18 weeks study, participants' final workload increased significantly to 38 ± 8 ($p < 0.001$) minutes at 29 ± 25 w ($p < 0.01$). Patients with ESRD previously have been reported to have low functional mobility (median TUG time, 12.21 seconds; 25th-75th percentiles, 8.7-13.6) (Jamal et al., 2006). Storer et al.'s (2005) participant cohort, aged 44 ± 9 years, scored 7.56 ± 2.43 seconds. In comparison, baseline TUG times observed in the 3 groups in the present study (Table 3) were no different from those previously reported for healthy similarly aged (50-59 years) individuals (6.44 ± 0.17s) (Isles et al., 2004). The lack of improvement in TUG could therefore be caused by limited room for improvement in the present study's "high-functioning" group in this measure when ESRD patients are concerned. However, it is possible that the lack of improvement in exercising patients also may have occurred because there was no functional strength training component in the exercise intervention.

There was no significant change observed in grip strength in any group over the intervention period. A previous study reported improvements in muscular strength in ESRD patients following resistance training (Headley et al., 2002). Following 12 weeks of progressive resistance training using machine weights that included eight to nine upper and lower body exercises such as the double leg press, leg curls, chest press and lateral raises for three sets at rating of perceived exertion of 10-12 in the 6-20 scale (Borg, 1998) they reported no significant changes in grip strength despite significant improvements in lower limb strength i.e. peak torque at 90° ($p<0.05$) over the intervention period. The authors did not provide a possible reason for the lack of change in grip strength following their training protocol but had probably included this measure due to the importance of this measure in performing functional activities of daily living and the fact that their training protocol included five upper body exercises out of the nine exercises in total. Hence, reasons other than exercise training have resulted in the lack of improvement in grip strength in the present study's treatment groups. A plausible reason might have been uremic neuropathy, a common condition in ESRD, which might have caused diminished motor control and therefore decreased strength in end-stage renal patients (Krishnan, 2007).

5.3 Self Reported Health

In contrast to changes observed in exercise capacity and physical activity, intradialytic exercise training resulted in significant decreases in self-reported physical functioning (Table 4.4). This decrease in the intradialytic-exercise group is difficult to explain. However, increased physical activity has been associated with decreased quality of life previously in healthy sedentary individuals (Halbert et al., 2000). There exists a small possibility that the SF-36, in the present study's patient cohort, was not sensitive enough to draw out changes in perceived quality of life. Using a content analysis from transcribed verbatim interview, improved performance in ADLs, positive change in haemodialysis experience, and enhanced sense of control were reported following eight weeks of intradialytic exercise (Kolewaski et al., 2005). Hence, positive changes that were not assessed via the SF-36 would have gone unobserved. It is also possible that the intradialytic nature of the exercise caused intradialytic exercise participants to associate the exercise with their ongoing treatment and therefore, although they experienced improvements in exercise capacity and physical activity, quality of life, including self-reported physical function, was influenced negatively by exercise being associated with the dialysis treatment.

5.4 Blood Pressure and Pulse Wave Velocity

Compared with usual care, there were no significant changes in PWV or AIx with either intradialytic or home based training, indicating that aerobic exercise training at the intensity, duration, and frequency prescribed may not benefit aortic stiffness or factors that decrease AIx (such as improved peripheral vasodilation) in patients with ESRD. These findings contrast with those of previous reports examining the effect of exercise training on arterial stiffness in patients with ESRD (Mustata et al., 2004, Toussaint et al., 2008b). Mustata et al. (2004) reported that AIx decreased significantly in eleven uncontrolled HD patients who attended 3 months of a twice-weekly outpatient aerobic exercise program. The decrease in AIx paralleled that of brachial pulse pressure, suggesting that large artery compliance may have been improved in response to training, although this is only speculation as neither regional or local arterial measures were acquired (Mustata et al., 2004). In contrast, there were no significant changes in AIx or pulse pressure in either treatment group during the intervention period in the current study. The reason for the contrasting findings is uncertain, but may relate to differences in initial blood pressures. Nineteen of the 46 patients had isolated systolic hypertension, and endurance training does not affect arterial compliance in older participants with this condition (Ferrier et al., 2001, Westhoff et al., 2007). When patients with isolated systolic hypertension were removed from this analysis, there were no significant changes in AIx in the intradialytic-exercise (+4%; 95% CI, -7.7 to 16.1; $p = 0.9$) or home-based-exercise group (+2%; 95% CI, -9.8 to 13.3; $p = 0.8$). Although this may be caused by the smaller sample ($n = 27$) remaining in the analysis, this is unlikely because of the small mean increase in AIx in both treatment groups and the range of within-group changes. Patients enrolled in the study of Mustata et al. (2004) may not have been hypertensive, although it is difficult to be certain because they reported only pulse pressure and did not measure PWV, thereby precluding a comparison to our primary outcome measure of arterial stiffness. In a recent crossover study, Toussaint et al. (2008) compared three months of intradialytic-exercise training with three months of usual care. Aortic PWV was found to decrease significantly. A methodological difference compared with the current study was the exercise intensity prescribed. Our study guided intradialytic exercise patients to train at 12-13 on the Borg RPE scale. In contrast, patients included in the study by Toussaint et al. (2008) determined their own levels of exertion and were not formally supervised. Although absolute intensity was not reported by Toussaint et al. (2008), average work performed per exercise session was approximately70 kcal. This compares with approximately 35kcal of work performed per session at the end of our protocol. Consequently, participants in the study by Toussaint et al. (2008) might have worked at a higher intensity or longer duration than those in our study, which may explain the disparate results.

The initial degree of arterial stiffness is another factor that may have contributed to the lack of change in vascular parameters after either exercise intervention. Adult patients with ESRD have aortic PWV that tends to be higher than in healthy age-, sex-, and blood pressure–matched controls (London et al., 1996). Although the patient group in the only previous study (Toussaint et al., 2008b) to examine the effect of exercise training on PWV in patients with ESRD, had baseline values (ranging from 9.8 ±3.8 to 10.4 ± 3.1m.s^{-1}) similar to those previously reported in patients with ESRD (London et al., 1996), baseline values of participants in the present study (8.27 ± 1.74 m.s^{-1}) were closer to those observed in healthy controls (London et al., 1996). It therefore is tempting to speculate that the lack of improvement in vascular parameters in the present study was caused by a smaller margin for improvement. However, this is unlikely because studies of healthy participants with aortic PWV similar to those reported in the present study have reported decreases after as few as 8 weeks of training at moderate intensities (Hayashi et al., 2005, Kakiyama et al., 2005). Arterial stiffness in healthy populations is highly correlated with age and activity levels (Vaitkevicius et al., 1993), however arterial stiffness in patients with ESRD is accelerated by metabolic imbalances (London et al., 2002). The range of potential contributors to arterial stiffness in ESRD is depicted below (Fig. 5.1). It is possible that arterial stiffness in ESRD is less responsive to exercise induced change due to the range of confounding factors. London et al. (2002) ascribed arterial stiffening in ESRD to various haemodynamic factors characteristic of ESRD. With regard to tensile and shear stress, London et al. (2002) suggested that while acute changes in tensile and shear stress may induce transient changes in vasomotor tone, chronic alterations as in chronic renal failure, would lead to longer lasting changes in vascular geometry and structure, which may be less responsive to exercise-induced changes in vasomotor tone over a period of six months.

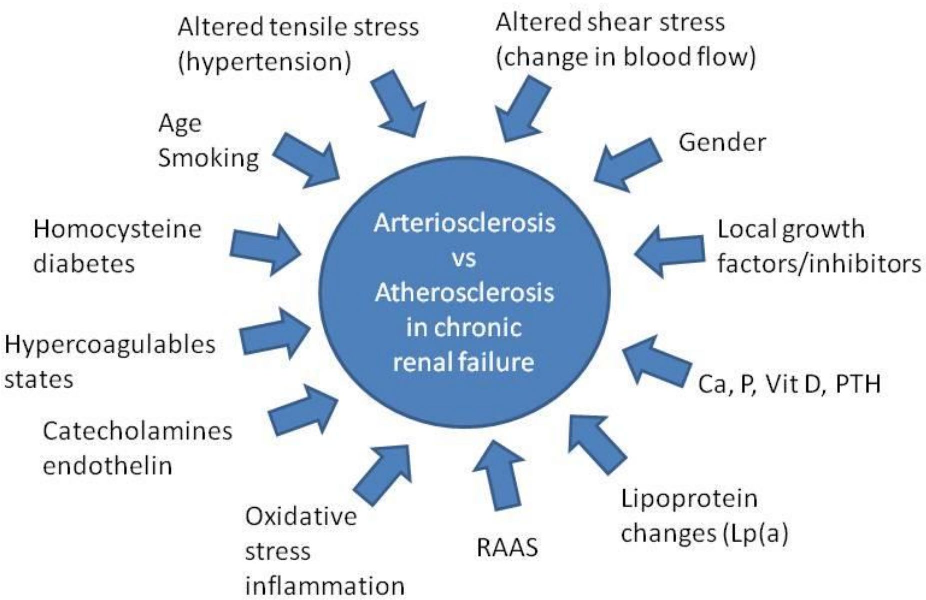

Figure 5.1 Schematic representation of pathogenic factors affecting arterial stiffness in chronic renal failure. [Taken from London et al., (2000) Arterial structure and function in ESRD, p. 1714.]

5.5 Limitations

There were two main limitations to this study that have reduced the chances of making clear conclusions about the effectiveness of intradialytic and home based exercise training on physical function and arterial health in ESRD. Each of these limitations is addressed in the following section.

5.5.1 Sample Size

A major limitation of this study was the failure of the sample-size calculation assumptions to be met. The present study's data indicated that the assumptions used in our sample-size calculation were not met and that 40 participants would be needed per group to achieve statistical significance for a clinically significant 10% improvement in 6-minute walk distance (β = 80%; α = 0.05). Data obtained in this study also indicated that 36 participants would be needed per group to attain statistical significance for a clinically significant improvement of -1.0 $m.s^{-1}$ in aortic PWV (Blacher et al., 1999) (β = 80%; α = 0.05). The assumed variability derived from other authors was lower than the variability observed in our population. Retrospective power analyses of the data indicate that this resulted in only 41% and 42% power for the primary outcome measures. A possible explanation for the lack of significance may be inferred from the mean improvements in the six-minute walk distance in the UC group. However while there was a reported 36% increase in physical activity in the UC group over the intervention period, the increase was still substantially lower than that observed in either of the training groups.

5.5.2. Control Group's Compliance

Despite regular reminders to the UC participants of the importance of maintaining their usual lifestyles with regards to physical activity, they might have still been inadvertently affected, and therefore motivated to increase their physical activity, by the patient educational brochure indicating the benefits of exercise which was provided to all patients at the beginning of the trial as a condition of approval by the ethics committee. In addition, the control participants might have been motivated to increase their own physical activity levels as they watched ID participants training within the same renal unit during their haemodialysis sessions. While UC group was regularly reminded to maintain their usual lifestyle, it was difficult to quantify any incidental physical activity that the UC group might have performed during the intervention period. It must also be acknowledged that while the investigators have reminded participants to maintain usual activities, changes to diet such as cutting out fast food or sugared beverages over the intervention period would have had an effect on the outcome measures of arterial stiffness. Such changes to diet were not measured and hence it remains a possible explanation for the greater than expected variability in results observed in the current study.

5.5.3 Familiarity to Assessment: Learning Effect of Repeated Testing

Another potential limitation in the present study was the possibility of learning effect from repeated trials of the 6MWT test. This must be considered due to the mean (+5%) increase in six-minute walk distance in the usual care group over the intervention period which reduced the likelihood of observing significant improvements in this measure in either treatment group. It has been reported that six-minute walk distances increase with sequential performance of the test as subjects learn how to optimally pace themselves in tests that were held two months apart (Wu et al., 2003). The reported regression showed a continuous improvement in the six-minute walk distance over six trials despite the absence of any intervention that would have altered participants' walking performances. The authors (Wu et al., 2003) suggested that this learning effect must be considered when using the six-minute walk as an assessment tool. A future consideration would be to follow the recommendation by Wu et al. (2003) to include three trials at each assessment time point, in order to obtain the longest distance achieved; however, this might be a challenge for physically limited ESRD patients. In the present study, to attempt to account for this learning effect, participants' underwent a practice run of the six-minute walk test several days prior to their baseline test. In addition there was a long period between the performance of the baseline test and the next occasion that participants underwent the test at 6 month testing. Thus it is considered unlikely that a learning effect was to blame but nevertheless, it must be considered. Another observation that Wu et al. (2003) made was the 'ceiling effect' where participants whose distances were higher at baseline encountered a situation where the distance covered could not be increased any further unless participants started to jog or run. In the current study the six-minute walk distance in the ID group was highest at baseline and endpoint testing and this group therefore could have been experiencing a 'ceiling effect'.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

The present study has examined the effects of 6 months of intradialytic exercise training and home-based unsupervised walking training on vascular function, physical functioning and patients' self-reported health in haemodialysis patients over three renal units spread across the state of Tasmania, Australia. The major findings were that 6-months of either intradialytic or home-based exercise training at the frequency, duration and intensity prescribed were unable to elicit statistically significant results in either physical function or arterial health in ESRD patients. As discussed, these results were due to two main limiting factors including the limited sample size and the learning effect of repeated testing.

6.1 Recommendations for Future Research

Future research investigating the effects of exercise on arterial stiffness in ESRD should consider the following aspects:

- Controlling for patient physical and disease-specific variables such as age, vintage, and comorbidities.
- Controlling for patients' physical activity levels and dietary intake 24-48 hours prior to assessments of arterial and physical functions.
- Investigating the potential benefits to exercise tolerance during dialysis by alleviating metabolic acidosis through increasing bicarbonate concentrations in dialysis solutions to aid buffering capacity of H^+/lactate.
- Measuring the variables post dialysis in order to control hydration status of all participants.Increasing the length of intervention exercise training programs.
- Recruiting larger numbers of patients to increase sample size.
- Adopting methods to address the possible learning effect of repeated testing.

6.1.1 Control of Renal Disease Related Variables

Variables such as age, vintage (time spent on haemodialysis treatment in years and months), causes of renal failure, comorbidities, and physical limitation could be more tightly controlled for using more stringent selection criteria which exclude certain age and vintage groups. As arterial compliance decreases with age, older age groups will naturally have lower arterial compliance compared to younger age groups, hence the tunica media and adventitia may be more resistant to changes brought about by exercise training in older ESRD patients compared to younger patients. A possible age group to examine could include only 30-50 year olds. Where a wide age group is to be examined, another possible permutation could be the inclusion of a cross-sectional analysis where participants are segregated and analysed by age groups, so that the rates and degrees of vascular response to exercise in various ESRD age groups may be determined. Vintage could also be considered. The process of accelerated arterial stiffness begins in 50 per cent of patients before ESRD. Patients with longer haemodialysis vintages could have developed severe and therefore potentially more irreversible vascular changes than patients that have only recently commenced haemodialysis due to the longer periods of chronic vascular calcification as well as metabolic imbalances which affect the structure of the endothelium (London et al., 2002).

Current comorbidities should also be used as part of the selection process. Diabetic patients have been observed to present increased arterial stiffness compared to their healthy counterparts, hence ESRD patients with diabetes may have an additional factor that accelerates arterial stiffness compared to non-complicated ESRD. Future studies may compare the responses to exercise in diabetic ESRD patients and non-diabetic ESRD patients to determine the influence of diabetes status on vascular responses. Hence, research questions should also be specific to other acute conditions such as trauma and infections, or to chronic conditions such as diabetes. Direct injury to the kidneys and subsequent loss of the kidney function may have fewer complications to other physiological systems, while kidney failure secondary to a chronic condition may exhibit greater comorbidities. Therefore, a consideration of the causes of renal failure should be made and the design of the study must delineate specific target groups within the ESRD populations. This may limit patients' eligibility; however, it will increase homogeneity.

6.1.2 Physical Function of Patients as Criteria for Eligibility

Activities of daily living as a measure of physical function and quality of life could be used to screen initially for patient suitability to participate, and secondly to separate groups of patients into either low or high physical functioning groups for more intensive analyses. Such studies may be able to examine the factors that affect improvements in physical function in low-functioning versus high-functioning patients and hence be able to determine the most suitable forms of exercise rehabilitation for different functioning levels.

6.1.3 Other Confounding Factors

In a similar vein, controls of pre-test variables that could potentially impact on arterial compliance and physical function should be put in place. Future studies must ensure that patients' physical activity participation, as well as dietary consumption, 24-48 hours prior to all testing times is controlled. The effects of alcohol consumption in some cases may affect arterial measures and physical performances. Excessive vigorous exercise prior to tests can elicit delayed onset of muscle soreness, which would affect physical function performance. Controlling for such factors would prevent any immediate causative influence on arterial compliance and physical function.

6.1.4 Larger Sample Sizes

A large, nation-wide study should be undertaken. If access to 10-15% of the 60,000 Australians that are suffering from ESRD each year could be made, the impact of the findings would achieve international regard and hence command authority in policy making at international levels. This large sample size would allow more room to accommodate for significant individual changes that could otherwise affect small sample groups. Medications and comorbidities could also be included as covariates in the statistical analyses which would reduce some of the limitations noted in the current study. This large study could also stratify geographic, socioeconomic, and other demographic differences may also be observed. It would be interesting to find out if renal units in the tropical i.e. northern areas would have the same results in terms or patient compliance to the training programs or if environmental factors such as climate, and therefore lifestyles may play a contributing factor to arterial stiffness.

6.1.5 Recommendations to Improve Intervention Effectiveness

6.1.5.a Exercise tolerance.

The low exercise tolerance in ESRD patients has caused one previous study (Storer et al., 2005) to lower exercise intensity in order for patients to tolerate the exercise training. In the present study, the participants in the intradialytic exercise training group's self selected intensity i.e. wattage on the Monark™ rehab trainer was similar to that observed in the study by Storer et al. (2005). Steps could be taken towards investigating the possibility of alleviating muscle soreness which may be achieved using interval training. Storer et al. (2005) adopted an interval-training approach where a one-minute rest was given to patients after every four minutes of exercise.

6.1.5 b Improving Home-Based Walking Programmes

As shown in the present study, a home-based walking program was feasible; however, the walking program may be better prescribed using accelerometers and heart rate monitors. Using this equipment, investigators may set specific speeds and intensities of walking as training goals, which could be self-monitored by patients. This may improve patients' motivation by having objective goals to work towards for each walking session. Such methods to set training goals and increase patients' motivation may enhance the effectiveness of the walking programme. The use of accelerometers may also be included as a method of measuring the work performed in the walking group. In addition, it may act as a motivational tool to progressively increase the number of steps or distance walked.

6.1.6 Length of intervention

Another recommendation addressing exercise intervention is the lengthening of the total duration of the exercise program from six months to nine or twelve months. This may allow patients more time in the first three months to become accustomed to the routine of including exercise training either during or outside of dialysis sessions. The following six or nine months could therefore allow investigators to include a more structured progressive training regime. As a result of this lengthening of the intervention, the first three months may be seen as an easing in period where patients prepare themselves to be trained further at intensities necessary to elicit positive vascular and physical functioning changes. With regard to arterial stiffness which has been found to be chronically increased in ESRD patients, such a longer term intervention may be warranted to deal with arterial stiffness caused by chronic renal diseases that may be more resistant to change. However, it may be unrealistic to expect patients to continue to participate for an additional three to six months and the labour intensive nature of such an approach would be expensive, hence careful planning must be performed prior to such an undertaking. A follow up of patients six months after the completion of the intervention may also be warranted to examine whether any benefits obtained during the intervention period are maintained over the longer term.

6.1.7 Recommendations to Improve Assessment Arterial Measures Reliability

Blood pressure measures and pulse wave measures should be performed immediately post-dialysis. Fluid overload in haemodialysis patients may affect pulse wave velocity as the increase in the volume of blood within the arteries may potentially increase circumferential stress within the endothelium. Such a change in pressure on the arterial wall may confer greater pressure wave velocity with each cardiac cycle. This step could potentially eliminate incidental influences such as hydration status on blood pressure and therefore arterial measures. Post-dialysis measures should be taken as all patients would be equally and optimally euhydrated. Hence, post-dialysis pulse wave measurements would exclude any possibility of increased blood pressures due to increased fluid volume between dialysis sessions, which may differ from session to session depending on patients' social, work or other personal commitments that may alter their usual diets and therefore fluid intake.

6.2 Conclusions

In conclusion, the present study suggests no benefit of regular exercise training in ESRD patients on either physical functioning or arterial health. However it seems likely that the intensity and duration of the present study's intradialytic and home-based exercise training, the small sample size and the possibility of the high-functioning levels of the patients resulting in a ceiling effect contributed to this result. Another possibility could be the unexpected mean increase in physical activity level of the usual care group over the period of the intervention period. Thus further studies are required to elucidate the effects of different modes and intensities of exercise training on vascular changes in ESRD.

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APPENDIX A:
Borg's (6-20) Rating of Perceived Exertion Scale

6	No exertion at all
7	Extremely light
8	
9	Very Light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (Heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

(Printed in A3 sheet for use during six-minute walk test)

APPENDIX B - Ethical Approval from Human Research Ethics Committee (Tasmania) Network

Tasmania
DEPARTMENT *of* HEALTH *and* HUMAN SERVICES

Human Research Ethics Committee (Tasmania) Network

UNIVERSITY OF TASMANIA

Northern Tasmania Health and Medical
Human Research Ethics Committee
APPLICATION APPROVAL

To:	Professor Rob Fassett
From:	Amanda McAully Executive Officer
Date:	17 December 2004
Subject:	H8124 Effects of Exercise Training on Arterial Stiffness in Haemodialysis Patients

The Northern Tasmania Health and Medical Human Research Ethics Committee on 17/12/2004 recommended approval of this project.

You are required to report immediately anything which might affect ethical acceptance of the project, including:

- serious or unexpected adverse effects on participants;
- proposed changes in the protocol;
- unforeseen events that might affect continued ethical acceptability of the project.

You are also required to inform the Committee if the project is discontinued before the expected date of completion, giving the reasons for discontinuation.

Please Note: Approval is subject to annual review. You will be asked to submit your first report on this project by 17/12/2005.

Regards,

RC Kovanovic
pp Amanda McAully

Contact: University of Tasmania
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Received 21.12.04.

APPENDIX C

Medical Outcomes Short-Form 36-items (SF-36) Health Survey

SF-36Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by circling the number or ticking the bubble that best represents your response.

Study ID: ____________Date: _____________ Person helping to complete this form: ____________________

1. In general, would you say your health is:
   - □ Excellent
   - □ Very good
   - □ Good
   - □ Fair
   - □ Poor

2. Compared to one year ago, how would you rate your health in general now?
   - □ Much better now than a year ago
   - □ Somewhat better now than a year ago
   - □ About the same as one year ago
   - □ Somewhat worse now than one year ago
   - □ Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
A	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
B	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
C	Lifting or carrying groceries	1	2	3
D	Climbing several flights of stairs	1	2	3
E	Climbing one flight of stairs	1	2	3
F	Bending, kneeling or stooping	1	2	3
G	Walking more than one mile	1	2	3
H	Walking several blocks	1	2	3
I	Walking one block	1	2	3
J	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down the amount of time you spent on work or other activities?

□ Yes □ No

b. Accomplished less than you would like? □ Yes □No

c. Were limited in the kind of work or other activities □ Yes □No

d. Had difficulty performing the work or other activities (For example, it took extra time) □ Yes □No

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down the amount of time you spent on work or other activities?
□Yes □ No

b. Accomplished less than you would like □ Yes □ No

c. Didn't do work or other activities as carefully as usual □ Yes □ No

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

□ Not at all
□ Slightly
□ Moderately
□ Quite a bit
□ Extremely

7. How much bodily pain have you had during the past 4 weeks?

□ Not at all
□ Slightly
□ Moderately
□ Quite a bit
□ Extremely

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

□ Not at all
□ Slightly
□ Moderately
□ Quite a bit
□ Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
A	did you feel full of pep?	1	2	3	4	5	6
B	have you been a very nervous person?	1	2	3	4	5	6
C	have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5	6
D	have you felt calm and peaceful	1	2	3	4	5	6
E	did you have a lot of energy?	1	2	3	4	5	6
F	have you felt downhearted and blue?	1	2	3	4	5	6
G	did you feel worn out?	1	2	3	4	5	6
H	have you been a happy person?	1	2	3	4	5	6
I	did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- □ All of the time
- □ Most of the time
- □ Some of the time
- □ A little of the time
- □ None of the time

11. How TRUE or FALSE is each of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
A	I seem to get sick a little easier than other people	1	2	3	4	5
B	I am as healthy as anybody I know	1	2	3	4	5
C	I expect my health to get worse	1	2	3	4	5
D	My health is excellent	1	2	3	4	5

==============End of Survey=========================

APPENDIX D

Active Australia Questionnaire

The Active Australia Survey

The next questions are about any physical activities that you may have done in the last
week:

1. In the last week, how many times have you walked continuously, for at least 10 minutes, for recreation, exercise or to get to or from places? ___________times

1a. What do you estimate was the total time that you spent walking in this way in the last week? In hours and/or minutes

_____hours_____minutes

2. In the last week, how many times did you do any vigorous gardening or heavy work around the yard, which made you breathe harder or puff and pant?
___________times

2a. What do you estimate was the total time that you spent doing vigorous gardening or
heavy work around the yard in the last week? In hours and/or minutes

_____hours_____minutes

The next questions exclude household chores, gardening or yardwork:

3. In the last week, how many times did you do any vigorous physical activity which made you breathe harder or puff and pant? (e.g. jogging, cycling, aerobics, competitive tennis) ____________times

3a. What do you estimate was the total time that you spent doing this vigorous physical activity in the last week? In hours and/or minutes

_____hours_____minutes

4. In the last week, how many times did you do any other more moderate physical activities that you have not already mentioned? (e.g. gentle swimming, social tennis, golf) ___________times

4a. What do you estimate was the total time that you spent doing these activities in the last week? (In hours and/or minutes)

_____hours_____minutes

=======================End of Survey========================